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Original article

Synthesis and biological activity of imidazopyridine anticoccidial agents: Part II

Andrew Scribner [a,*], Richard Dennis [a], Shuliang Lee [a], Gilles Ouvry [a], David Perrey [a], Michael Fisher [b], Matthew Wyvratt [b], Penny Leavitt [c], Paul Liberator [c], Anne Gurnett [c], Chris Brown [c], John Mathew [c], Donald Thompson [c], Dennis Schmatz [c], Tesfaye Biftu [b]

[a] *SCYNEXIS, Inc., Discovery Chemistry, P.O. Box 12878, Research Triangle Park, NC 27709-2878, USA*
[b] *Department of Medicinal Chemistry, Merck Research Laboratories, Merck & Co., Inc., Rahway, NJ 07065, USA*
[c] *Department of Human and Animal Infectious Disease Research, Merck Research Laboratories, Merck & Co., Inc., Rahway, NJ 07065, USA*

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Abstract

Coccidiosis is the major cause of morbidity and mortality in the poultry industry. Protozoan parasites of the genus *Eimeria* invade the intestinal lining of the avian host causing tissue pathology, poor weight gain, and in some cases mortality. Resistance to current anticoccidials has prompted the search for new therapeutic agents with potent in vitro and in vivo activity against *Eimeria*. Recently, we reported the synthesis and biological activity of potent imidazo[1,2-*a*]pyridine anticoccidial agents. Antiparasitic activity is due to inhibition of a parasite specific cGMP-dependent protein kinase (PKG). In this study, we report the synthesis and anticoccidial activity of a second set of such compounds, focusing on derivatization of the amine side chain at the imidazopyridine 7-position. From this series, several compounds showed subnanomolar in vitro activity and commercial levels of in vivo activity. However, the potential genotoxicity of these compounds precludes them from further development.

Keywords: Coccidiosis; Antiparasitic; Antiprotozoal; Kinase; Imidazopyridine

1. Introduction

Coccidiosis is a parasitic disease which is the major cause of morbidity and mortality in the poultry industry. It is a disease of the avian intestinal lining due to invasion by protozoan parasites of the genus *Eimeria* [1]. Some of the most significant *Eimeria* species in poultry are *Eimeria tenella*, *Eimeria acervulina*, *Eimeria necartrix*, *Eimeria brunetti, Eimeria mitis*, and *Eimeria maxima*. Over 35 billion chickens are raised annually worldwide, and all major poultry operations use anticoccidial agents prophylactically. Resistance to current coccidiostats is becoming widespread, and new broad spectrum drugs directed at novel biochemical targets are needed. Genetic studies in *Toxoplasma gondii*, a protozoan parasite closely related to *Eimeria*, demonstrate that cGMP-dependent protein kinase (PKG) is essential for survival and represents a desirable therapeutic target [2]. It was reported recently that inhibition of a novel PKG, isolated from these parasites, stops the parasite proliferation by blocking parasite invasion [2,3]. High throughput screening of known kinase inhibitors resulted in the discovery of imidazopyridine analogs as PKG inhibitors and broad spectrum anticoccidial agents [4]. Recently, we reported the synthesis and biological activity of imidazo[1,2-*a*]pyridines with diversity introduced at the 2-aryl and 3-aryl rings [4,5]. Herein, we report PKG inhibition, synthesis, evaluation, optimization, and in vivo anticoccidial activities of imidazopyridines possessing optimal functionality at the 2-aryl and 3-aryl rings, and with diversity introduced at the amine side chain of the imidazopyridine 7-position.

* Corresponding author. Tel.: +919 544 8610; fax: +919 544 8697.
E-mail address: andrew.scribner@scynexis.com (A. Scribner).

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2. Results and discussions

2.1. Chemistry

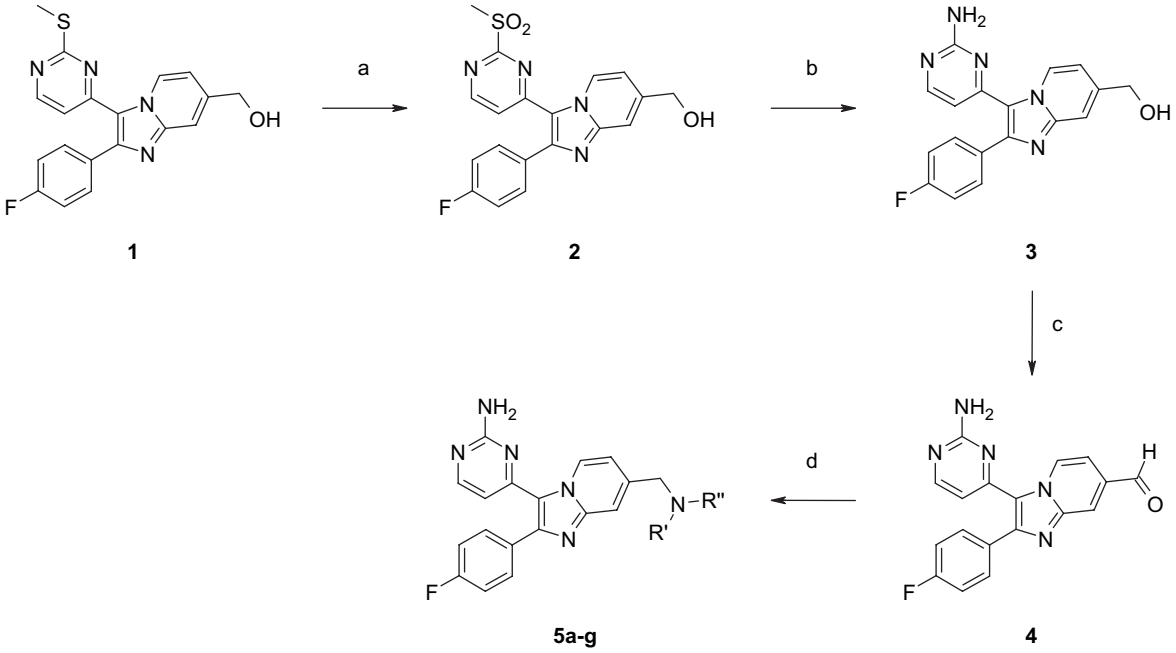
Introduction of functionality on a benzylic amine nitrogen at the imidazopyridine 7-position was accomplished as shown in Scheme 1. The synthesis of sulfide **1** is presented in a companion publication [5]. Oxidation of sulfide **1** with OXONE® gave sulfone **2**. Subsequent treatment with ammonia afforded 2-aminopyrimidine **3**. Oxidation of the benzylic alcohol with manganese(IV) oxide yielded aldehyde **4** [6]. Treatment of **4** with various amines and sodium triacetoxyborohydride ultimately yielded benzylic amines **5a–g** [7].

Syntheses of compounds bearing a carbonyl group bridging the imidazopyridine 7-position to the benzylic amine are shown in Schemes 2 and 3. In Scheme 2, treatment of aldehyde **4** with hydroxylamine and trifluoroacetic acid gave nitrile **6** [8], which was hydrolyzed with potassium hydroxide to yield amide **7** [9]. Alternatively, nitrile **6** was converted to imidate **8** when treated with ethanol and hydrochloric acid [10]. Subsequent treatment of imidate **8** with dimethylamine gave amidine **9** [10]. An unexpected byproduct of this reaction was *N*,*N*-dimethylaniline **10**, which presumably resulted from elimination of ethanol from imidate **8** to give a 7-cyanoimidazopyridine, followed by dimethylamine displacement of the cyano group.

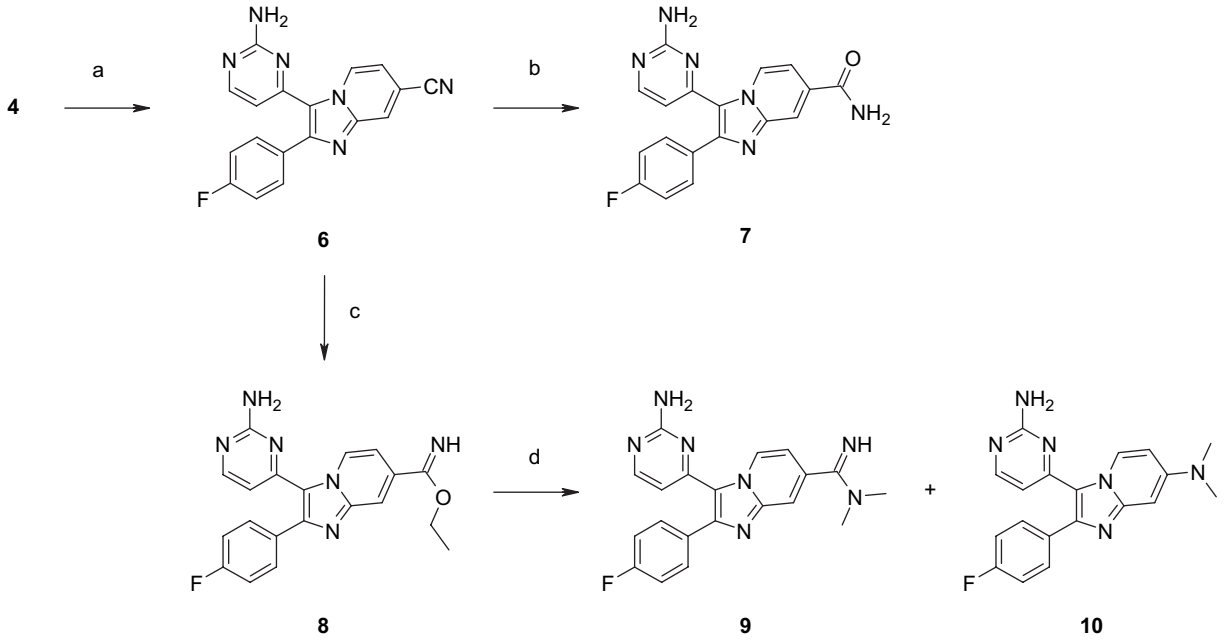
Synthesis of the corresponding 7-carboxylic acid methyl amide (**17**) is shown in Scheme 3. The synthesis of bromide **11** is presented in a companion publication [5]. Subsequent cyclization with 2-(amino)isonicotinic acid ethyl ester yielded imidazopyridine **12** [11], which upon treatment with *N*,*O*-dimethylhydroxylamine hydrochloride and isopropylmagnesium chloride gave Weinreb amide **13** [12]. Oxidation of the sulfide group of **13** with OXONE® afforded sulfone **14**, which was treated with ammonia to give 2-aminopyrimidine **15** [13]. The reaction of Weinreb amide **15** with ethylmagnesium bromide gave both the expected ethyl ketone **16** [12], and 7-carboxylic acid methyl amide **17**, which likely arises from deprotonation of the Weinreb amide methoxy group by the Grignard reagent followed by E2 elimination of formaldehyde [14].

Different pathways were used to introduce one or two alkyl substituents at the benzylic carbon of a 7-(dimethylaminomethyl)imidazopyridine, shown in Schemes 4 and 5. Synthesis of analogs in which this alkyl group is a single methyl or ethyl is shown in Scheme 4. Oxidation of alcohol **1** with manganese(IV) oxide gave aldehyde **18** [6], which was treated with methylmagnesium bromide to give secondary alcohol **20a**. Similarly, treatment of Weinreb amide **13** with ethylmagnesium bromide gave ethyl ketone **19** [12], which was reduced with sodium borohydride to give alcohol **20b**. Esterification of alcohols **20a** and **20b** with methanesulfonyl chloride and triethylamine yielded methanesulfonate esters **21a** and **21b**, which was followed by treatment with dimethylamine and diisopropylethylamine to give benzylic dimethylamines **22a** and **22b**. Oxidation of sulfides **22a** and **22b** to sulfones **23a** and **23b** was performed with either OXONE® or peracetic acid and catalytic sodium tungstate hydrate, followed by treatment with sulfur dioxide to reduce any tertiary amine oxide back to the tertiary amine [15]. Subsequent displacement of sulfone by ammonia then followed to ultimately yield 2-aminopyrimidines [13] **24a** and **24b**. HPLC separation of enantiomers of **24a** was conducted on a Chiralcel OJ (Diacel) column.

A slightly different approach was used to introduce either an *n*-propyl chain or two geminal methyl groups onto the benzylic



Scheme 1. Reagents: (a) OXONE®; (b) NH_3; (c) MnO_2; (d) HNR′R″, $NaB(OAc)_3H$ where R′ and R″ are defined as part of the R substituent of compounds **5a–g** in Table 1.



Scheme 2. Reagents: (a) NH_2OH, CF_3CO_2H; (b) KOH; (c) EtOH, HCl; (d) $HNMe_2$.

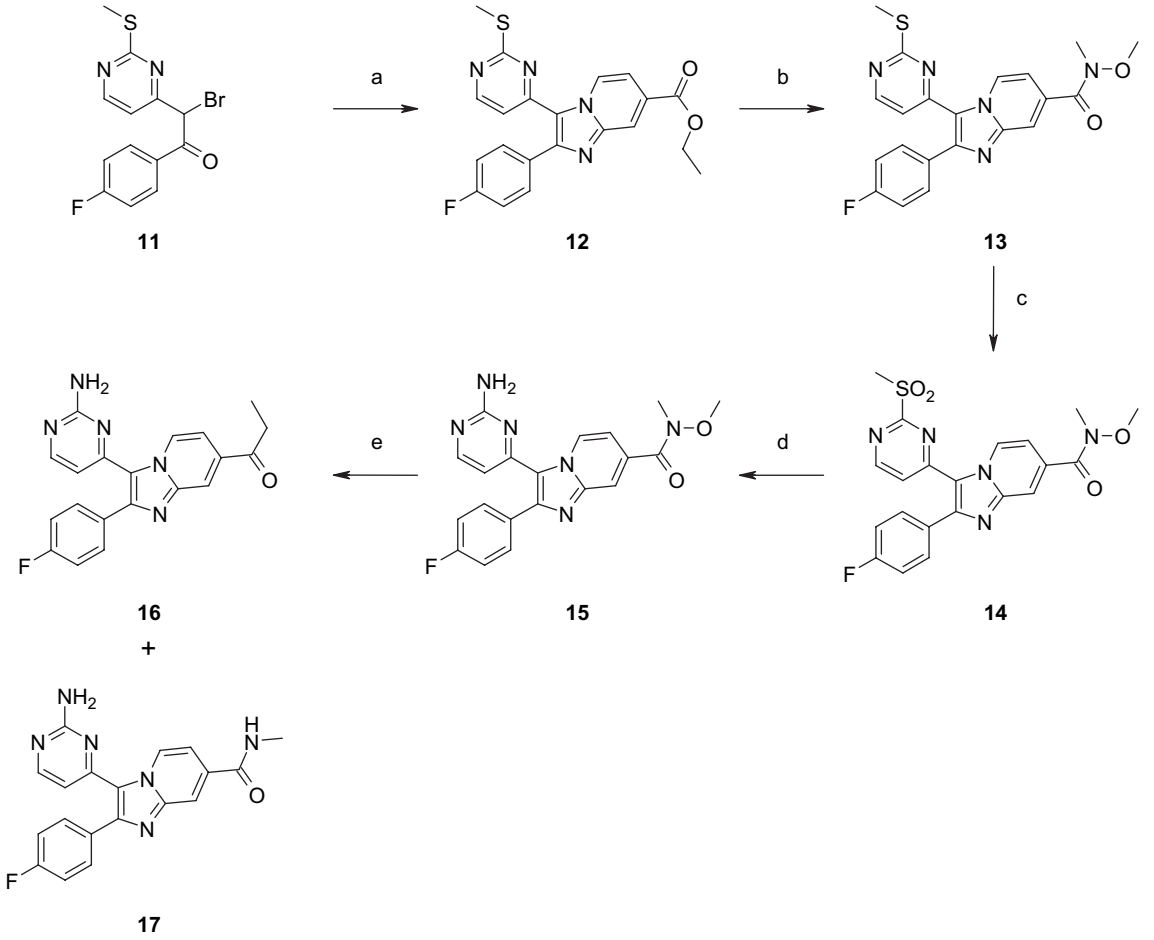
carbon (Scheme 5). Methanesulfonate **25** (prepared in a companion publication) [5] was treated with tetra-*n*-butylammonium cyanide to yield nitrile **26** [16], which was then alkylated with 1-bromopropane to give α-*n*-propylnitrile **27a** [17], or excess iodomethane to give *gem*-dimethylnitrile **27b** [18]. Subsequent hydrolysis with concentrated sulfuric acid yielded amides **28a** and **28b**, which underwent Hofmann rearrangement with bis(trifluoroacetoxy)iodobenzene to afford primary amines **29a** and **29b** [19]. Reductive amination with formaldehyde and sodium cyanoborohydride with catalytic acetic acid afforded dimethylamines **30a** and **30b** [20]. Functionalization of the pyrimidine 2-position ensued as described earlier, entailing oxidation of sulfides **30a** and **30b** to sulfone **31a** and **31b** with OXONE® followed by back-reduction of any N-oxide with sulfur dioxide [15], and ammonia displacement of this sulfone to ultimately yield 2-aminopyrimidines **32a** and **32b** [13].

An alternative pathway to introduce two geminal methyl groups onto the benzylic carbon is shown in Scheme 6. Treatment of ester **12** with excess methylmagnesium bromide gave tertiary alcohol **33** [21]. Functionalization of the pyrimidine 2-position followed, as treatment of sulfide **33** with OXONE® gave sulfone **34**, which was then treated with ammonia to yield 2-aminopyrimidine **35** [13]. Treatment of tertiary alcohol **35** with Ritter conditions (sodium cyanide, acetic acid, and sulfuric acid) gave a mixture of formamides **36a** and **36b**, which was hydrolyzed with sodium hydroxide to ultimately yield *gem*-dimethyl primary amine **37** [22].

The synthesis of 7-(dimethylamino)ethylimidazopyridines is shown in Schemes 7 and 8. Scheme 7 shows the synthesis of 7-(dimethylamino)ethylimidazopyridines **42a–c**. Alkylation of nitrile **26** with ethyl bromide and sodium hydride yielded α-ethylnitrile **38** [17]. Oxidation of sulfides **26**, **38**, and **27b** to sulfones **39a–c**, respectively, was achieved with OXONE®. At this point, different routes and reagents were explored for each substrate. Nitriles **39a** and **39b** were first reduced via hydrogenation with catalytic platinum(IV) oxide [23] to give primary amines **40a** and **40b**. Displacement of the sulfones with ammonia gave 2-aminopyrimidines **41a** and **41b** [13]. Alternatively, sulfone **39c** was first treated with ammonia to give 2-aminopyrimidine **40c**, whose nitrile was then reduced via lithium aluminum hydride [24] to give primary amine **41c**; both of these routes towards intermediates **41a–c** proved viable. Subsequent reductive amination with formaldehyde, sodium cyanoborohydride, and catalytic acetic acid ultimately yielded 7-(dimethylamino)ethylimidazopyridines **42a–c** [20].

The synthesis of a 7-(dimethylamino)ethylimidazopyridine bearing a fluorine at the benzylic carbon is shown in Scheme 8. Refluxing aldehyde **18** with sarcosine and paraformaldehyde resulted in a [3 + 2] cycloaddition to give aminal **43**, which was then cleaved open upon treatment with sodium borohydride to give the benzylic alcohol **44** [25]. Subsequent treatment with DAST gave fluoride **45** [26]. Oxidation of sulfide **45** with OXONE® followed by back-reduction with sulfur dioxide to give sulfone **46** [15]. Treatment with ammonia ultimately yielded 2-aminopyrimidine **47** [13].

The synthesis of 7-(dimethylamino)-*n*-propylimidazopyridine **55** is shown in Scheme 9. Treatment of 2-chloro-4′-fluoroacetophenone with *O*-methylhydroxylamine hydrochloride gave α-chloro-*O*-methyloxime **48** [27], which upon treatment with lithium bromide yielded α-bromo-*O*-methyloxime **49**. Subsequent reaction of 4-propanolpyridine with **49** under basic conditions afforded imidazopyridine **50** [27]. Esterification with methanesulfonyl chloride gave methanesulfonate ester **51**, and subsequent treatment with dimethylamine and diisopropylethylamine yielded dimethylamine **52**. Acylation then occurred with acetic anhydride and catalytic sulfuric acid to give ketone **53** [28], which was activated with *N*,*N*-dimethylformamide



Scheme 3. Reagents: (a) 2-(amino)isonicotinic acid ethyl ester; (b) Me(MeO)NH·HCl, *i*-PrMgCl; (c) OXONE®; (d) NH_3; (e) CH_3CH_2MgBr.

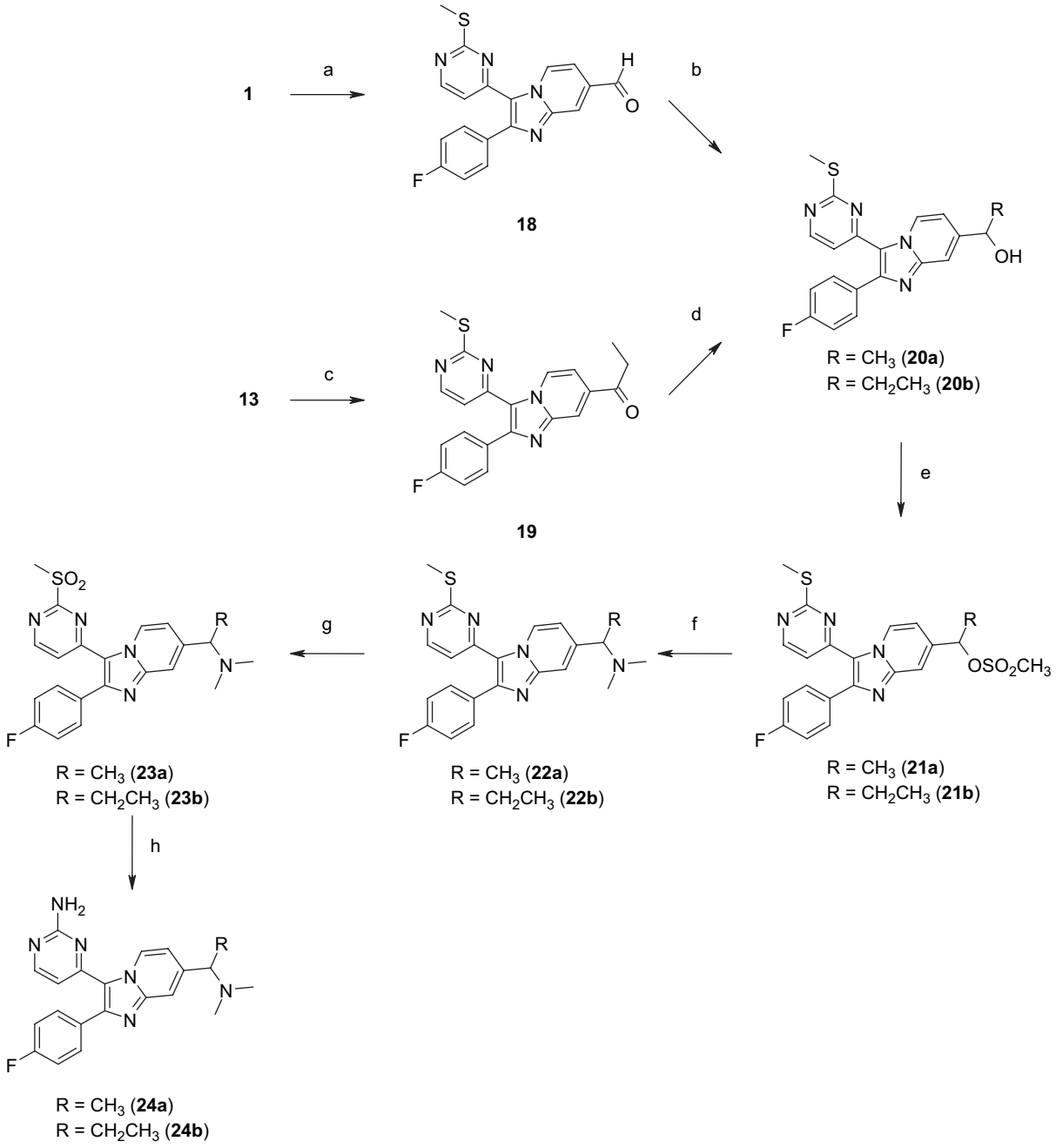
dimethyl acetal (DMFDMA) to afford enone **54** [29]. Treatment with guanidine hydrochloride and sodium methoxide ultimately yielded 2-aminopyrimidine **55** [29].

The pathway used to prepare 7-(piperidinyl)imidazopyridines is shown in Scheme 10. First, protection of the piperidine nitrogen of 4-piperidin-4-ylpyridine occurred with acetic anhydride to give acetamide **56**. Subsequent treatment with α-bromo-*O*-methyloxime **49** followed by base afforded imidazopyridine **57** [27]. Acylation of the imidazopyridine 3-position occurred with acetic anhydride and catalytic sulfuric acid to give ketone **58** [28]. Reaction of this with DMFDMA then afforded enone **59** [29], which upon treatment with guanidine hydrochloride and sodium methoxide yielded 2-aminopyrimidine **60** [29]. Subsequent hydrolysis of the acetamide protecting group with hydrochloric acid gave NH-piperidine **61**, which then underwent reductive amination with appropriate aldehyde or alkylation with appropriate alkyl halide under basic conditions to ultimately yield *N*-alkylpiperidines **62a–k** [20].

Synthesis of 7-(piperazinyl)imidazopyridine **67** is shown in Scheme 11. Treatment of 2-bromo-4′-fluoroacetophenone with 2-amino-4-chloropyridine [30] afforded 7-chloroimidazopyridine **63** [11] which was acylated to ketone **64** with acetic anhydride and catalytic sulfuric acid [28]. Reaction of this ketone with DMFDMA gave enone **65** [29], which was followed by treatment with guanidine hydrochloride and sodium methoxide to afford 2-aminopyrimidine **66** [29]. Treatment of 7-chloroimidazopyridine **66** with palladium(II) acetate, 2-(di-*tert*-butylphosphino)biphenyl, sodium *tert*-butoxide, and *N*-methylpiperazine ultimately yielded 7-(*N*-Me-piperazin-4-yl) imidazopyridine **67** [28,31].

2.2. Biology

The title compounds were tested for in vitro efficacy via the Ten_K (*Ten*ella *K*inase) assay, and in vivo efficacy via the ExMAC (*Ex*panded *M*ini-*A*ssay *C*occidiosis) assay. The Ten_K assay measures inhibition of *E. tenella* PKG enzyme activity, and is reported as the amount of compound required to inhibit activity by 50% (IC_{50}, in nM). The ExMAC assay measures antiparasitic activity after administration of compound to infected chickens (ppm in feed). Birds are infected with *E. tenella* (E_t), *E. acervulina* (E_a), *E. mitis* (E_{mi}), and *E. maxima* (E_{ma}), and efficacy is reported using a score of 0 through 4 based on percent of oocyte reduction relative to an untreated control. Treatments that provide 100% reduction of oocyte production are scored with a '4', those with 99% reduction are scored '3+', those with 80–98% reduction are scored '3', those with 50–79% reduction are scored '2', and those with <50% reduction are scored '0'. Details of these

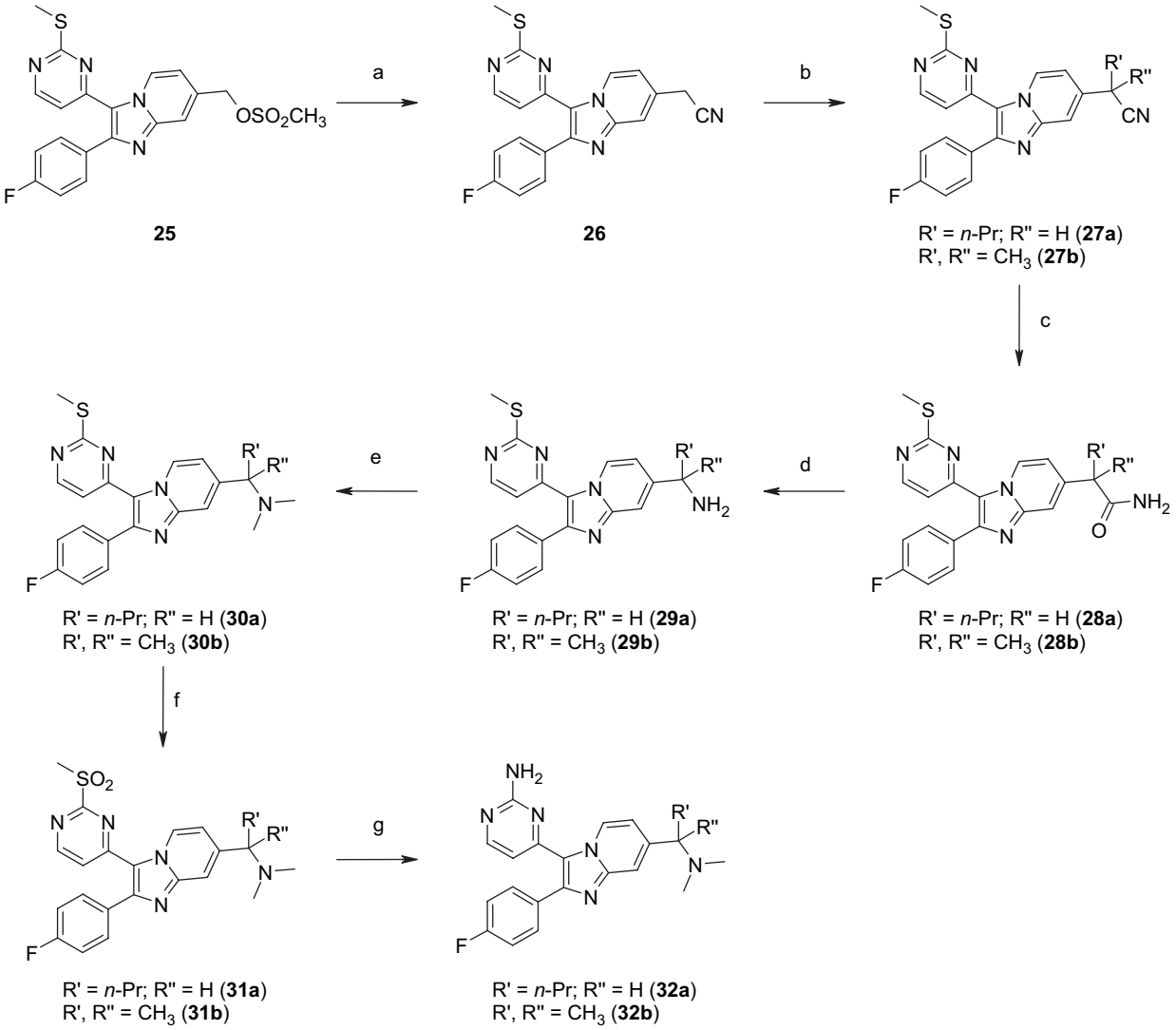


Scheme 4. Reagents: (a) MnO_2; (b) CH_3MgBr; (c) CH_3CH_2MgBr; (d) $NaBH_4$; (e) CH_3SO_2Cl, Et_3N; (f) $HNMe_2$, *i*-Pr_2NEt; (g) i. OXONE® or 30% H_2O_2, AcOH, $Na_2WO_4 \cdot 2H_2O$; ii. SO_2; (h) NH_3.

procedures were published in earlier work [3]. In some cases, not all four species of *Eimeria* were tested.

The data presented in Table 1 summarize the effect on both in vitro and in vivo activity of modifying substituents on the benzylic amine at the imidazopyridine 7-position relative to our benzylic dimethylamine lead compound (**68**), which we have reported previously [4a]. Other than nitrile **5e** and piperazine **5g**, all compounds from this set showed subnanomolar in vitro activity except for those lacking a basic nitrogen on the side chain of the imidazopyridine 7-position (amides **7** and **17**, and amidine **9**). Likewise, in vivo efficacy was considerably weaker in these same compounds lacking a basic amine on the side chain. In fact, only dimethylamine **68** and diethylamine **5f** exhibited significant in vivo activity at 12.5 ppm, suggesting that both basicity and minimal steric bulk at the amine nitrogen are crucial for in vivo potency.

Table 2 shows the biological effect of varying the length of the side chain tethering the imidazopyridine 7-postion to the amine nitrogen. The in vitro data suggest that there is considerable tolerance for amine side chains of different lengths, with subnanomolar activity seen in compounds possessing a chain of one, two, or three carbons (compounds **68**, **42a**,



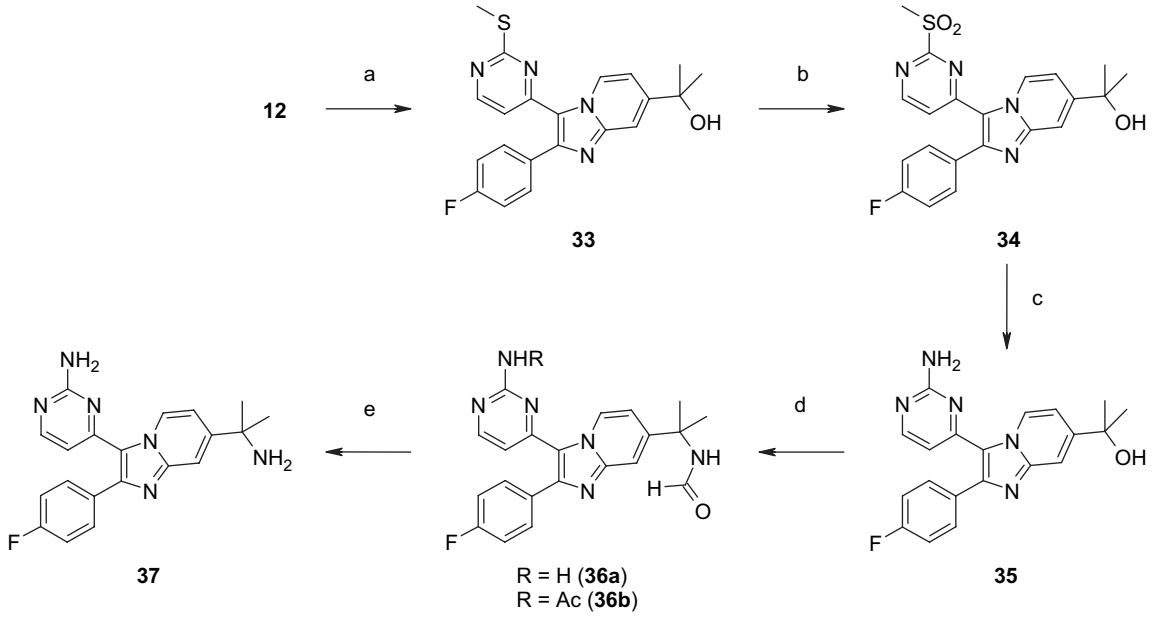
Scheme 5. Reagents: (a) n-Bu_4NCN; (b) $CH_3CH_2CH_2Br$ or CH_3I; NaH; (c) H_2SO_4; (d) $PhI(OCO_2CF_3)_2$; (e) H_2CO, $NaBH_3CN$, AcOH; (f) i. OXONE®; ii. SO_2; (g) NH_3.

and **55**, respectively). The *N*,*N*-dimethylaniline **10** may have weaker in vitro activity due to the lack of a basic nitrogen, as discussed for examples **7**, **9**, and **17** in Table 1. In vivo potency was found to be optimal in the analogs possessing a one or two carbon chain (compounds **68** and **42a**).

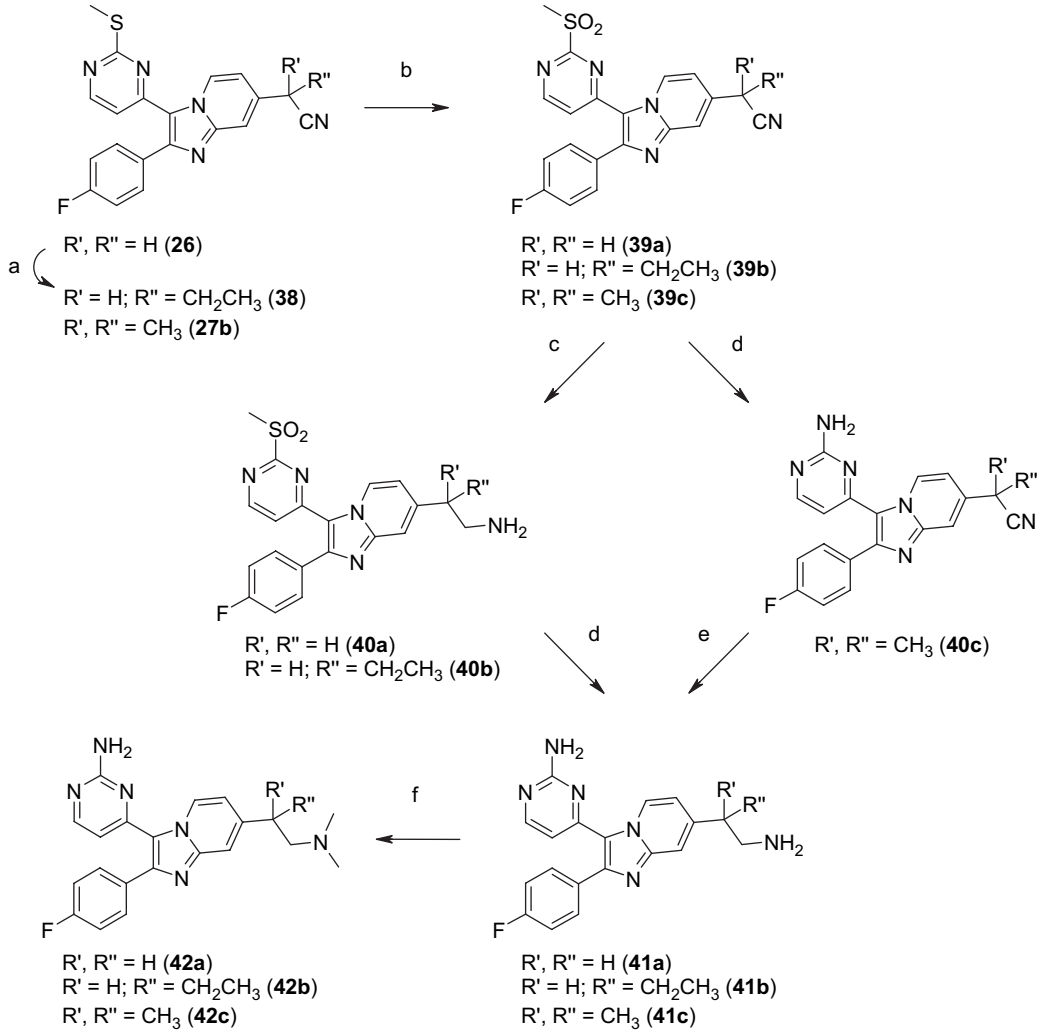
Table 3 shows the effect of substituents on the alkyl chain tethering the imidazopyridine 7-position to the amine nitrogen. Each benzylic amine (**24a**, **24b**, **32a**, **37**, and **32b**) exhibited subnanomolar activity in vitro, and in some cases (**24a**, **32a**) showed an $IC_{50} < 0.1$ nM. Introducing one alkyl substituent at the benzylic carbon increased in vivo activity when the substituent was methyl (**24a**, particularly enantiomer B, active vs. all four *Eimeria* species in vivo down to 2 ppm) and ethyl (**24b**). The *n*-propyl analog (**32a**) also showed strong in vitro activity, but weaker in vivo potency. When two geminal methyl groups were introduced at the benzylic carbon (**37**, **32b**), the in vivo activity slightly increased in the case of the tertiary dimethylamine (**32b**).

Regarding the homobenzylic amines (**42a**, **42b**, **41c**, **42c**, and **47**), in vitro potency remained subnanomolar in each case. In vivo activity was optimal with the unsubstituted homobenzylic amine **42a** and the fluoride **47**. All other examples with larger substituents on the side chain showed weaker in vivo potency.

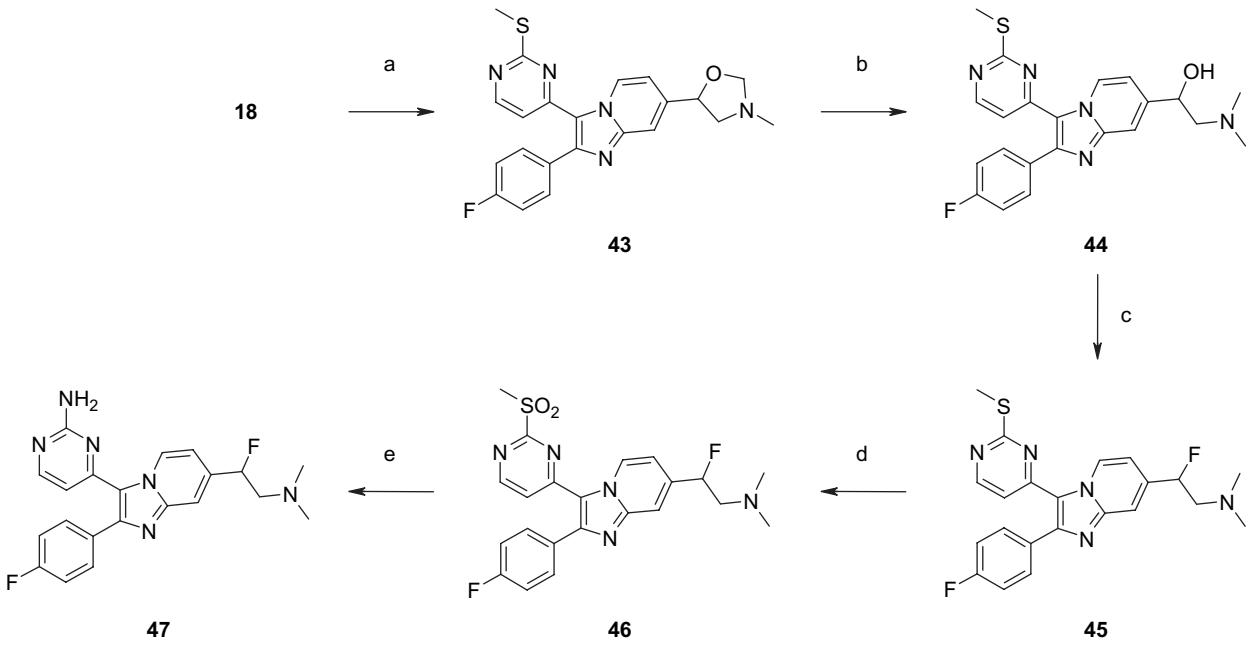
After observing promising activity with alkyl branching at the benzylic carbon of the imidazopyridine 7-position, we then explored the effect of combining this branching with an entropically restricted side chain nitrogen. Table 4 shows the effect of having a 6-membered amine-bearing ring (piperidine or piperazine) at the imidazopyridine 7-position. All such compounds tested showed subnanomolar in vitro potency, and in several cases (**61**, **69**, **62b**, **62c**, **62e**, and **62k**) showed an $IC_{50} < 0.1$ nM. Although the straight-chain analog possessing a 3-carbon tether (**55**, described in Table 2) exhibited relatively weak in vivo potency, many of these piperidines showed excellent activity in vivo, especially compounds in which the *N*-substituent was methyl (**69**, previously published) [4], ethyl (**62a**), hydroxyethyl (**62b**), isobutyl (**62d**), and cyclopropylmethyl (**62e**). Larger, more lipophilic *N*-substituents decreased in vivo potency. The 7-*N*-methylpiperazine (**67**) showed



Scheme 6. Reagents: (a) CH_3MgBr; (b) OXONE®; (c) NH_3; (d) NaCN, AcOH, H_2SO_4; (e) NaOH.



Scheme 7. Reagents: (a) NaH, CH_3CH_2Br; (b) OXONE®; (c) H_2, PtO_2; (d) NH_3; (e) $LiAlH_4$; (f) H_2CO, $NaBH_3CN$, AcOH.



Scheme 8. Reagents: (a) $H_3CN(H)CH_2CO_2H$, $(CH_2O)_n$; (b) $NaBH_4$; (c) DAST; (d) i. OXONE®; ii. SO_2; (e) NH_3.

greater in vivo activity that the other dialkylaniline tested (**10**) which does not possess as basic a nitrogen in the side chain; however, **67** was not as potent as the corresponding *N*-methylpiperidine (**69**).

3. Conclusion

We have prepared several 2-aryl-3-(2-aminopyrimidin-4-yl) imidazopyridines with varying alkyl amine substitution on the imidazopyridine 7-position as anticoccidial agents. We have found that there is considerable tolerance for varying the chain length between the imidazopyridine 7-position and the amine from one to two to three carbons, and for introducing one or two additional alkyl groups on the benzylic carbon. We have also found tolerance in vitro for steric bulk at the 7-position, although in vivo efficacy begins to decrease as the size and lipophilicity of the substituent increases. The most active compounds from this series showing in vivo potency against all four species of *Eimeria* at or below 12.5 ppm include monoalkylated benzylic amines **24a** (enantiomeric mixture and enantiomer B) and **24b**, gem-dialkylated benzylic amine **32b**, homobenzylic amines **42a** and **47**, and piperidines **62a**, **62b**, **62d**, and **62e**. However, the potential genotoxicity of compounds in this series precluded them from further development [4].

4. Experimental sections

4.1. General

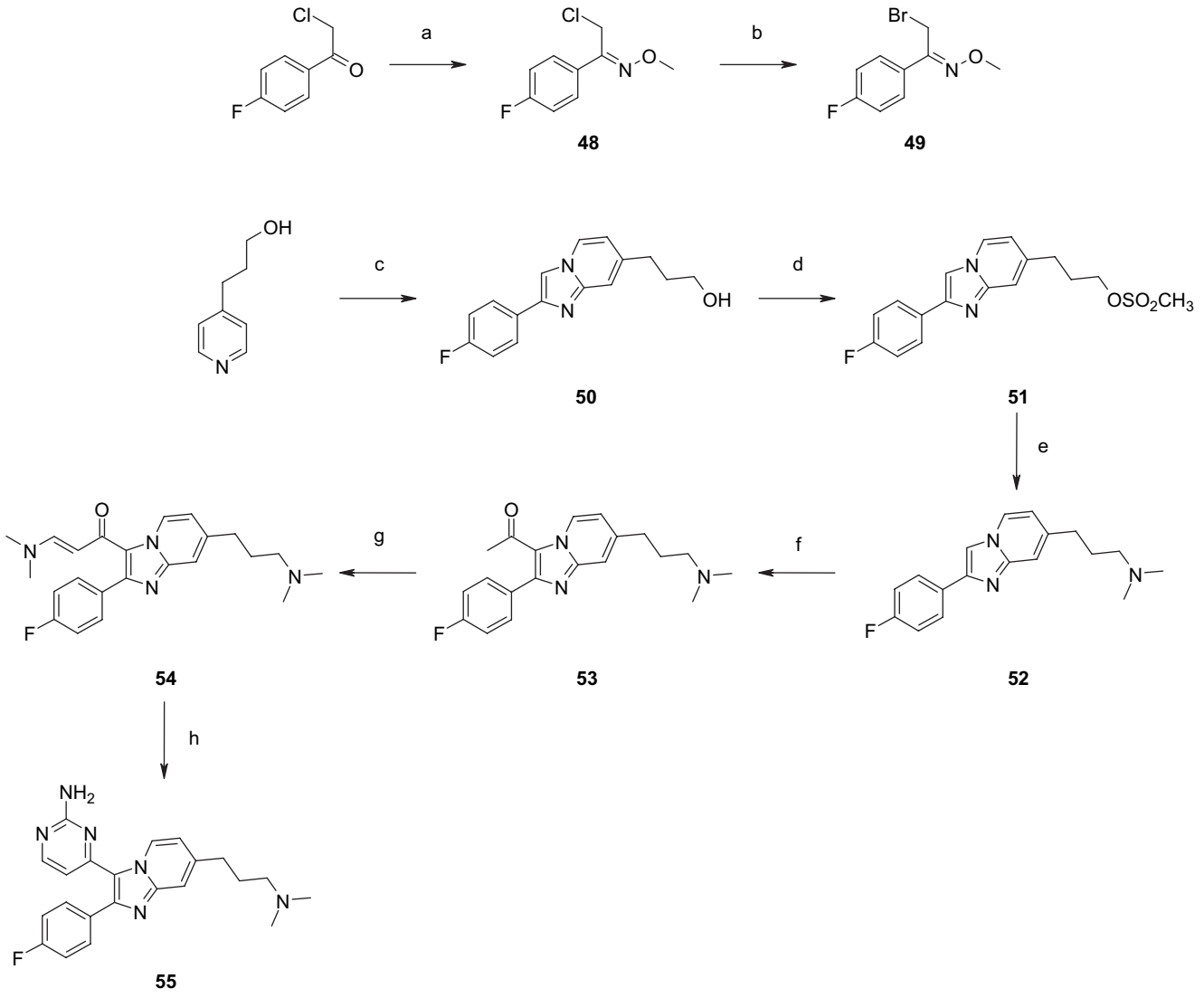
Reactions were monitored by thin-layer chromatography (TLC) on precoated EMD silica gel (60 F_{254}) plates (250 μm thickness) and visualized using UV light (254 nm), or by LCMS using a ThermoFinnigan AQA spectrometer with UV detection (254 nm). Flash chromatography purification was performed using Isco RediSep cartridges on an Isco OptiX10 or Companion automated flash chromatography system, or using EMD silica gel (230–400 mesh). HPLC purification was conducted on a Varian Dynamax HPLC Guard Column, 21.4 mm, Compression Module Microsorb Guard-8C-18 (P/N R00083221G). ^{1}H NMR spectra were recorded on a Varian Unity INOVA 400 MHz spectrometer; the values of chemical shifts (δ) are given in parts per million relative to the central peak of the solvent, and the values of coupling constants (J) are given in hertz (Hz). Mass spectra were recorded on a ThermoFinnigan AQA spectrometer. HPLC traces were recorded on an Agilent 1100 or Hewlett Packard 1050 instrument with a Phenomenex Aqua C18 125A 5 mm column, 4.6 mm i.d. × 50 mm length. All compounds tested biologically were found to be ≥90% pure by HPLC at 254 nM.

4.1.1. [2-(4-Fluorophenyl)-3-(2-methanesulfonylpyrimidin-4-yl)imidazo[1,2-a]pyridin-7-yl]methanol (2)

Sulfide **1** (2.80 g, 7.64 mmol) was suspended in MeOH (170 mL), acetone (140 mL), and an aqueous solution of OXONE® (14.1 g, 22.9 mmol, in 130 mL H_2O), and allowed to stir for 12 h. The reaction was then concentrated under reduced pressure to approximately 100 mL, then diluted with water (200 mL), filtered, and dried in a vacuum oven at 40 °C overnight. Yield of **2**: 2.35 g (77%) of **5**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.20 (s, 3H), 4.83 (s, 2H), 7.04–7.44 (m, 4H), 7.53–7.76 (m, 2H), 7.87 (bs, 1H), 8.62 (d, $J = 5.4$ Hz, 1H), 9.82 (d, $J = 7.0$ Hz, 1H). MS (ESI+) 398.8.

4.1.2. [3-(2-Aminopyrimidin-4-yl)-2-(4-fluorophenyl)-imidazo[1,2-a]pyridin-7-yl]methanol (3)

A mixture of sulfone **2** (14.4 g, 36.1 mmol) in THF (200 mL) in a pressure reactor was chilled to less than −70 °C in a CO_2/IPA bath. Ammonia (33.1 g, 1.94 mol) was



Scheme 9. Reagents: (a) $H_2NOCH_3 \cdot HCl$; (b) LiBr; (c) i. **49**; ii. DBU; (d) CH_3SO_2Cl, Et_3N; (e) $HNMe_2$, *i*-Pr_2NEt; (f) Ac_2O, H_2SO_4; (g) DMFDMA; (h) guanidine·HCl, NaOMe.

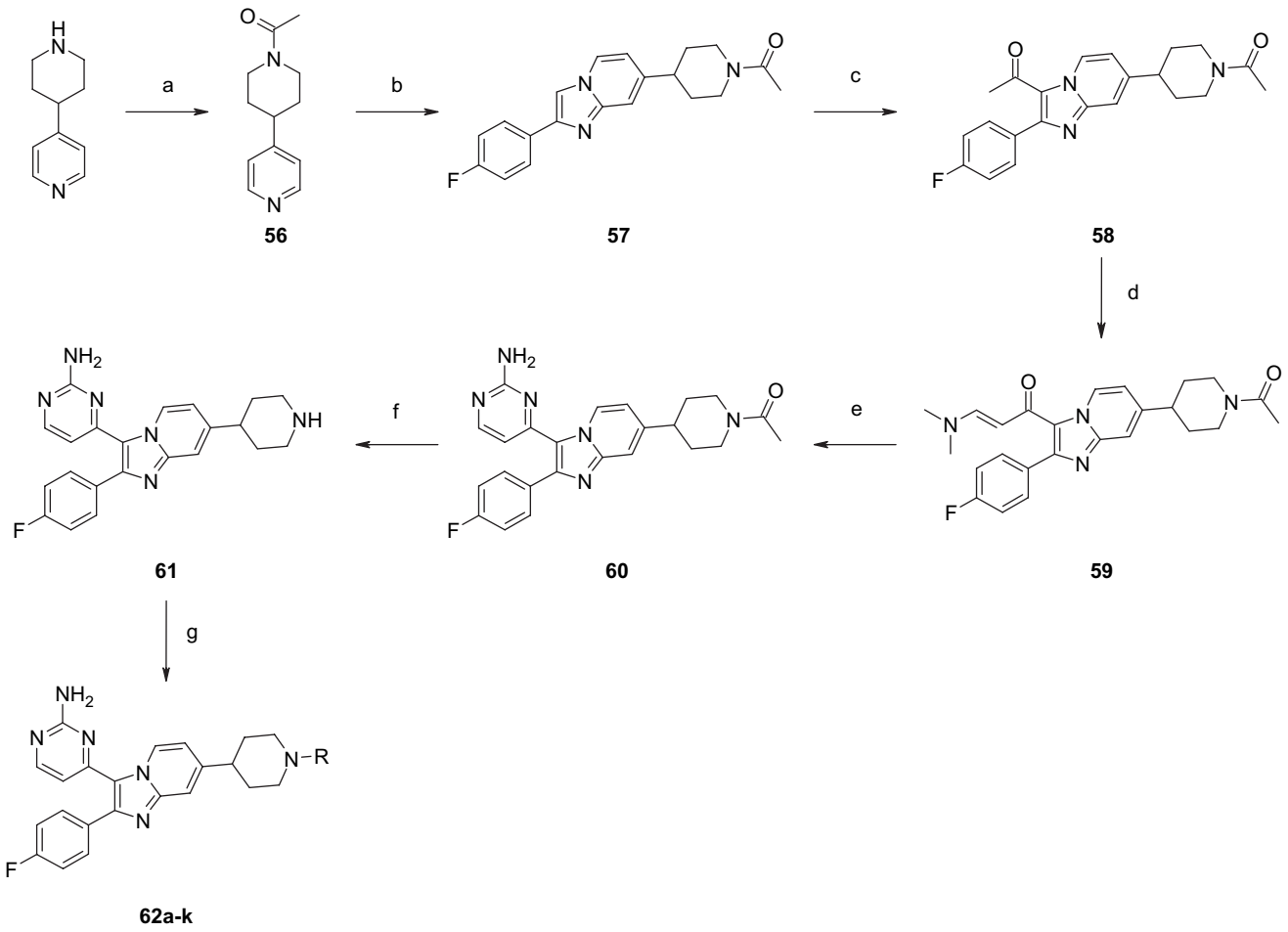
then bubbled in over 15 min. The pressure reactor was then sealed, and the reaction was allowed to warm to room temperature and stirred for 12 h, during which the reaction pressure reached 55 psi. The pressure was then released, and the reaction was concentrated under reduced pressure, then chromatographed on SiO_2 using a gradient that started with CH_2Cl_2 and ended with 90:9:1 CH_2Cl_2:MeOH:concentrated NH_4OH. Yield of **3**: 10.6 g (83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.74 (s, 2H), 5.06–5.25 (bs, 2H), 6.50 (d, $J = 5.4$ Hz, 1H), 6.88 (dd, $J = 7.2$, 1.6 Hz, 1H), 7.12 (t, $J = 8.7$ Hz, 2H), 7.53–7.73 (m, 3H), 8.12 (d, $J = 5.4$ Hz, 1H), 9.38 (d, $J = 7.2$ Hz, 1H). MS (ESI+) 336.0.

*4.1.3. [3-(2-Aminopyrimidin-4-yl)-2-(4-fluorophenyl)-imidazo[1,2-a]pyridine-7-carbaldehyde (**4**)*

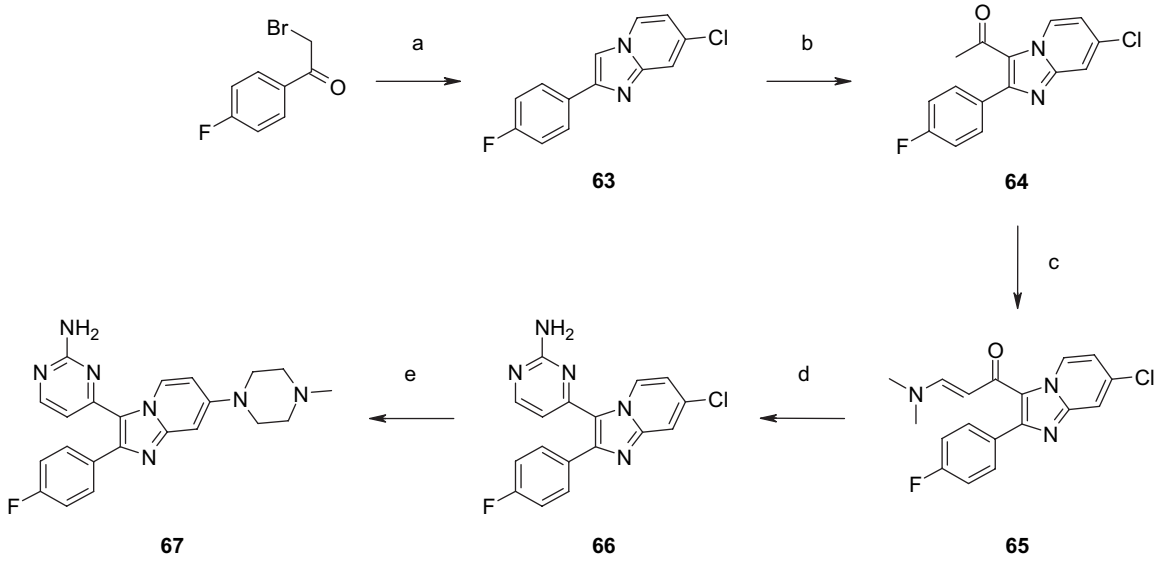
A solution of alcohol **3** (10.7 g, 31.9 mmol) in CH_2Cl_2 (1.0 L) was charged with manganese(IV) oxide (69.4 g, 798 mmol). The reaction was stirred at room temperature for 12 h, and was then filtered through Celite, and the Celite filter cake was then rinsed with 9:1 CH_2Cl_2:MeOH (9:1) (500 mL). The filtrates were combined, concentrated under reduced pressure, and not purified further. Yield of **4**: 7.8 g (74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.22 (bs, 2H), 6.57 (d, $J = 5.3$ Hz, 1H), 7.16 (t, $J = 8.7$ Hz, 2H), 7.43 (dd, $J = 7.2$, 1.6 Hz, 1H), 7.67 (m, 2H), 8.17 (s, 1H), 8.22 (d, $J = 5.3$ Hz, 1H), 9.46 (d, $J = 7.2$ Hz, 1H), 10.06 (s, 1H). MS (ESI+) 334.2.

*4.1.4. General procedure for the synthesis of tertiary amines **5a–g***

A solution of aldehyde **4** in CH_2Cl_2 was charged with appropriate amine and sodium triacetoxyborohydride. After stirring at room temperature for 12 h, the reaction was concentrated under reduced pressure, chromatographed on SiO_2 using a gradient that started with CH_2Cl_2 and ended with 90:9:1 CH_2Cl_2:MeOH:concentrated NH_4OH, and then purified further

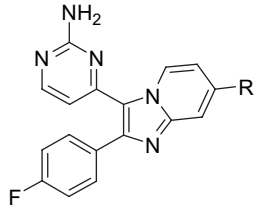


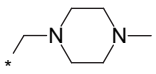
Scheme 10. Reagents: (a) Ac_2O; (b) i. **49**; ii. *t*-BuOK; (c), Ac_2O, H_2SO_4; (d) DMFDMA; (e) guanidine·HCl, NaOMe; (f) HCl; (g) appropriate aldehyde, $NaBH_3CN$, AcOH or RBr, K_2CO_3 where R is defined in Table 4.



Scheme 11. Reagents: (a) i. 2-amino-4-chloropyridine; ii. *t*-BuOK; (b), Ac_2O, H_2SO_4; (c) DMFDMA; (d) guanidine·HCl, NaOMe; (e) $Pd(OAc)_2$, 2-(di-*tert*-butylphosphino)biphenyl, *t*-BuONa, *N*-Me-piperazine.

Table 1
Biological activity of 7-substituted imidazopyridines: benzylic amines



Compound	R	Ten_K IC_{50} (nM)[a]	ExMAC dose (ppm)	ExMAC rating			
				E_t	E_a	E_{mi}	E_{ma}
68	$CH_2N(CH_3)_2$	0.11	25	3	3	3	3
			12.5	3	3	3	3
			6.25	3	3	0	0
5a	$CH_2NHC(CH_3)_3$	0.35; 0.68	ND				
5b	$CH_2N(CH_3)CH_2CH_2OH$	0.5	12.5	0	0	0	0
5c	$CH_2N(CH_3)CH_2CH_2OCH_3$	0.69	12.5	0	0	0	0
5d	$CH_2N(CH_3)CH_2C{\equiv}CH$	0.65	12.5	0	0	0	0
5e	$CH_2N(CH_3)CH_2C{\equiv}N$	1.33	25	3	3	0	0
5f	$CH_2N(CH_2CH_3)_2$	0.17; 0.42	25	3	2	3	3
			12.5	3	2	0	3
			6.25	0	0	2	0
5g		2.2	25	3	0	3	3
			12.5	0	0	0	0
7	$C(=O)NH_2$	1.8	50	3	0	0	2
9	$C(=NH)N(CH_3)_2$	2.5	25	0	2	0	0
17	$C(=O)NHCH_3$	3.1	25	0	0	0	2

[a] In cases where a compound was tested more than once, all values obtained are reported.

by HPLC using a MeOH/H_2O gradient, where the aqueous phase was 98.9:1.0:0.1 H_2O:CH_3CN:Et_3N.

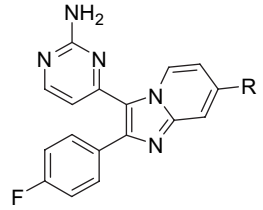
*4.1.4.1. 4-[7-tert-Butylaminomethyl)-2-(4-fluorophenyl)imidazo-[1,2-a]pyridin-3-yl]pyrimidin-2-ylamine (**5a**).* Amine **5a** was prepared from aldehyde **4** (100 mg, 0.300 mmol), *tert*-butylamine (33 mg, 47 μL, 0.45 mmol), and sodium triacetoxyborohydride (95 mg, 0.45 mmol) in CH_2Cl_2 (100 mL). Yield of **5a**: 42.9 mg (37%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (s, 9H), 3.84 (s, 2H), 5.12 (bs, 2H), 6.52 (d, $J = 5.4$ Hz, 1H), 7.00 (dd, $J = 7.2$, 1.5 Hz, 1H), 7.12 (t, $J = 8.7$ Hz, 2H), 7.59–7.70 (m, 3H), 8.11 (d, $J = 5.4$ Hz, 1H), 9.42 (d, $J = 7.2$ Hz, 1H). MS (ESI+) 391.1.

*4.1.4.2. 2-{[3-(2-Aminopyrimidin-4-yl)-2-(4-fluorophenyl)-imidazo[1,2-a]pyridin-7-ylmethyl]methylamino}ethanol (**5b**).* Amine **5b** was prepared from aldehyde **4** (100 mg, 0.300 mmol), 2-(methylamino)ethanol (34 mg, 36 μL, 0.45 mmol), and sodium triacetoxyborohydride (95 mg, 0.45 mmol) in CH_2Cl_2 (100 mL). Yield of **5b**: 27.7 mg (23%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33 (s, 3H), 2.69 (t, $J = 4.7$ Hz, 2H), 3.62–3.76 (m, 4H), 5.13 (bs, 2H), 6.53 (d, $J = 5.3$ Hz, 1H), 6.97–7.03 (m, 1H), 7.13 (t, $J = 8.7$ Hz, 2H), 7.58 (bs, 1H), 7.61–7.71 (m, 2H), 8.13 (d, $J = 5.3$ Hz, 1H), 9.46 (d, $J = 7.2$ Hz, 1H). MS (ESI+) 393.1.

*4.1.4.3. 4-(2-(4-Fluorophenyl)-7-{[(2-methoxyethyl)methyl-amino]methyl}imidazo[1,2-a]pyridin-3-yl)pyrimidin-2-ylamine (**5c**).* Amine **5c** was prepared from aldehyde **4** (100 mg, 0.300 mmol), *N*-(2-methoxyethyl)methylamine (40 mg, 48 μL, 0.45 mmol), and sodium triacetoxyborohydride (95 mg, 0.45 mmol) in CH_2Cl_2 (100 mL). Yield of **5c**: 44.6 mg (37%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35 (s, 3H), 2.64–2.75 (m, 2H), 3.38 (s, 3H), 3.53–3.60 (m, 2H), 3.68 (bs, 2H), 5.10 (bs, 2H), 6.53 (d, $J = 5.4$ Hz, 1H), 7.02–7.08 (m, 1H), 7.13 (t, $J = 8.7$ Hz, 2H), 7.58 (bs, 1H), 7.61–7.69 (m, 2H), 8.13 (d, $J = 5.4$ Hz, 1H), 9.42 (d, $J = 7.2$ Hz, 1H). MS (ESI+) 407.4.

*4.1.4.4. 4-{2-(4-Fluorophenyl)-7-[(methylprop-2-ynylamino)-methyl]imidazo[1,2-a]pyridin-3-yl}pyrimidin-2-ylamine (**5d**).* Amine **5d** was prepared from aldehyde **4** (100 mg, 0.300 mmol), *N*-methylpropargylamine (31 mg, 37 μL, 0.45 mmol), and sodium triacetoxyborohydride (95 mg, 0.45 mmol) in CH_2Cl_2 (100 mL). Yield of **5d**: 48.3 mg (42%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.31 (t, $J = 2.2$ Hz, 1H), 2.39 (s, 3H), 3.37 (d, $J = 2.2$ Hz, 2H), 3.67

Table 2
Biological activity of 7-substituted imidazopyridines: amine side chains of varying length



Compound	R	Ten_K IC_{50} (nM)[a]	ExMAC dose (ppm)	ExMAC rating			
				E_t	E_a	E_{mi}	E_{ma}
10	$N(CH_3)_2$	3	25	3	3	0	3
			12.5	2	0	0	3
			6.25	0	0	0	0
68	$CH_2N(CH_3)_2$	0.11	25	3	3	3	3
			12.5	3	3	3	3
			6.25	3	3	0	0
42a	$CH_2CH_2N(CH_3)_2$	0.46; 0.62	25	4	4	4	4
			12.5	4	4	3	4
			6.25	4	3	0	2
55	$CH_2CH_2CH_2N(CH_3)_2$	0.27	25	3	3	3	4
			12.5	3	3	0	0
			6.25	0	0	0	0

[a] In cases where a compound was tested more than once, all values obtained are reported.

(s, 2H), 5.14 (bs, 2H), 6.53 (d, $J = 5.3$ Hz, 1H), 7.01 (dd, $J = 7.2$, 1.5 Hz, 1H), 7.13 (t, $J = 8.7$ Hz, 2H), 7.62 (bs, 1H), 7.60–7.70 (m, 2H), 8.13 (d, $J = 5.3$ Hz, 1H), 9.42 (d, $J = 7.2$ Hz, 1H). MS (ESI+) 387.4.

*4.1.4.5. {[3-(2-Aminopyrimidin-4-yl)-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-7-ylmethyl]methylamino}acetonitrile (**5e**).* Amine **5e** was prepared from aldehyde **4** (100 mg, 0.300 mmol), methylaminoacetonitrile (32 mg, 34 μL, 0.45 mmol), and sodium triacetoxyborohydride (95 mg, 0.45 mmol) in CH_2Cl_2 (100 mL). Yield of **5e**: 19.5 mg (17%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.48 (s, 3H), 3.56 (s, 2H), 3.72 (s, 2H), 5.15 (bs, 2H), 6.53 (d, $J = 5.3$ Hz, 1H), 6.95 (dd, $J = 7.2$, 1.5 Hz, 1H), 7.13 (t, $J = 8.7$ Hz, 2H), 7.61–7.68 (m, 2H), 7.64 (bs, 1H), 8.14 (d, $J = 5.3$ Hz, 1H), 9.45 (d, $J = 7.2$ Hz, 1H). MS (ESI+) 388.3.

*4.1.4.6. 4-[7-Diethylaminomethyl-2-(4-fluorophenyl)imidazo-[1,2-a]pyridin-3-yl]pyrimidin-2-ylamine (**5f**).* Amine **5f** was prepared from aldehyde **4** (100 mg, 0.300 mmol), diethylamine (33 mg, 47 μL, 0.45 mmol), and sodium triacetoxyborohydride (95 mg, 0.45 mmol) in CH_2Cl_2 (100 mL). Yield of **5f**: 39.2 mg (34%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (t, $J = 7.0$ Hz, 6H), 2.58 (q, $J = 7.0$ Hz, 4H), 3.65 (s, 2H), 5.11 (bs, 2H), 6.53 (d, $J = 5.4$ Hz, 1H), 7.00–7.07 (m, 1H), 7.12 (t, $J = 8.7$ Hz, 2H), 7.62 (bs, 1H), 7.62–7.68 (m, 2H), 8.12 (d, $J = 5.4$ Hz, 1H), 9.41 (d, $J = 7.2$ Hz, 1H). MS (ESI+) 391.1.

*4.1.4.7. 4-[2-(4-Fluorophenyl)-7-(4-methylpiperazin-1-ylmethyl)-imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-ylamine (**5g**).* Amine **5g** was prepared from aldehyde **4** (100 mg, 0.300 mmol), *N*-methylpiperazine (45 mg, 60 μL, 0.45 mmol), and sodium triacetoxyborohydride (95 mg, 0.45 mmol) in CH_2Cl_2 (100 mL). Yield of **5g**: 72.2 mg (58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (s, 3H), 2.40–2.69 (m, 8H), 3.60 (s, 2H), 5.12 (bs, 2H), 6.52 (d, $J = 5.4$ Hz, 1H), 7.00 (dd, $J = 7.2$, 1.4 Hz, 1H), 7.12 (t, $J = 8.7$ Hz, 2H), 7.62 (bs, 1H), 7.63–7.76 (m, 2H), 8.13 (d, $J = 5.4$ Hz, 1H), 9.42 (d, $J = 7.2$ Hz, 1H). MS (ESI+) 418.2.

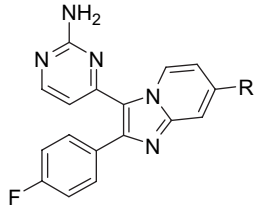
*4.1.5. 3-(2-Aminopyrimidin-4-yl)-2-(4-fluorophenyl)-imidazo[1,2-a]pyridine-7-carbonitrile (**6**)*

A solution of aldehyde **4** (1.20 g, 3.60 mmol) in trifluoroacetic acid (50 mL) was charged with hydroxylamine hydrochloride (375 mg, 5.40 mmol) and 4 Å molecular sieves, and heated to 85 °C for 15 h. The reaction was then cooled to room temperature and neutralized with the slow addition of saturated aqueous $NaHCO_3$ solution (600 mL), then extracted into 9:1 CH_2Cl_2:MeOH (5 × 200 mL), dried over Na_2SO_4, concentrated under reduced pressure, and then chromatographed on SiO_2 using a gradient that started with CH_2Cl_2 and ended with 90:9:1 CH_2Cl_2:MeOH:concentrated NH_4OH. Yield of **6**: 590 mg (50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.19 (bs, 2H), 6.57 (d, $J = 5.3$ Hz, 1H), 7.06 (dd, $J = 7.3$, 1.6 Hz, 1H), 7.16 (t, $J = 8.7$ Hz, 2H), 7.66–7.74 (m, 2H), 8.08 (bs, 1H), 8.22 (d, $J = 5.3$ Hz, 1H), 9.54 (d, $J = 7.3$ Hz, 1H). MS (ESI+) 331.1.

*4.1.6. 3-(2-Aminopyrimidin-4-yl)-2-(4-fluorophenyl)-imidazo[1,2-a]pyridine-7-carboxylic acid amide (**7**)*

Nitrile **6** (150 mg, 0.454 mmol) was slurried in 1-propanol (25 mL), then charged with KOH (56.0 mg, 1.00 mmol) and heated to 110 °C for 12 h. The reaction was then concentrated under reduced pressure, and then chromatographed on SiO_2 using a gradient that started with CH_2Cl_2 and ended with 90:9:1

Table 3
Biological activity of 7-substituted imidazopyridines: branched amine side chains



Compound	R	Ten_K IC_{50} (nM)[a]	ExMAC dose (ppm)	ExMAC rating			
				E_t	E_a	E_{mi}	E_{ma}
68	$CH_2N(CH_3)_2$	0.11	25	3	3	3	3
			12.5	3	3	3	3
			6.25	3	3	0	0
24a	$CH(CH_3)N(CH_3)_2$	0.09	6.25	4	4	4	4
			3.1	4	3	3	4
	$CH(CH_3)N(CH_3)_2$ enantiomer A	0.44; 0.28	4	3	3	0	0
			2	0	0	0	2
			1	2	0	2	2
	$CH(CH_3)N(CH_3)_2$ enantiomer B	0.087; 0.067	4	3	3	3	4
			2	3	4	3	3
			1	2	3	0	4
24b	$CH(CH_2CH_3)N(CH_3)_2$	0.13; 0.3	12.5	4	4	4	4
			8	2	3	0	2
32a	$CH(CH_2CH_2CH_3)N(CH_3)_2$	0.065	25	4	4	4	4
			12.5	0	3	0	0
			6.25	0	3	0	4
37	$C(CH_3)_2NH_2$	0.145; 0.26	12	4	3	0	4
			6	3	3	0	3
			3	0	2	0	3
32b	$C(CH_3)_2N(CH_3)_2$	0.11	8	4	4	0	4
			6.25	4	4	3	3
42a	$CH_2CH_2N(CH_3)_2$	0.46; 0.62	25	4	4	4	4
			12.5	4	4	3	4
			6.25	4	3	0	2
42b	$CH(CH_2CH_3)CH_2N(CH_3)_2$	0.4	25	4	0	0	4
41c	$C(CH_3)_2CH_2NH_2$	0.26	25	2	0	2	0
42c	$C(CH_3)_2CH_2N(CH_3)_2$	0.2	25	4	3	3	0
			12.5	3	3	0	0
			6.25	0	0	0	0
47	$CHFCH_2N(CH_3)_2$	0.59	25	4	4	4	4
			12.5	3	3	2	4
			6.25	3	0	0	4

[a] In cases where a compound was tested more than once, all values obtained are reported.

CH_2Cl_2:MeOH:concentrated NH_4OH. Yield of **7**: 42.0 mg (25%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.47 (d, $J = 5.6$ Hz, 1H), 7.15 (t, $J = 8.6$ Hz, 2H), 7.53 (dd, $J = 7.3$, 1.6 Hz, 1H), 7.56–7.64 (m, 2H), 8.06 (d, $J = 5.6$ Hz, 1H), 8.16 (bs, 1H), 9.54 (d, $J = 7.3$ Hz, 1H). MS (ESI+) 348.9.

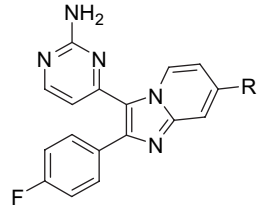
*4.1.7. 3-(2-Aminopyrimidin-4-yl)-2-(4-fluorophenyl)-imidazo[1,2-a]pyridine-7-carboximidic acid ethyl ester (**8**)*

A solution of nitrile **6** (430 mg, 1.30 mmol) in EtOH (200 mL) was cooled to 0 °C in an ice water bath, then charged with HCl gas for 30 min. The reaction was then allowed to warm to room temperature while stirring for 12 h, and was then concentrated under reduced pressure, and carried onto the next step without further purification. MS (ESI+) 376.2.

*4.1.8. 3-(2-Aminopyrimidin-4-yl)-2-(4-fluorophenyl)-N,N-dimethylimidazo[1,2-a]pyridine-7-carboxamidine (**9**) and 3-(2-aminopyrimidin-4-yl)-2-(4-fluorophenyl)imidazo[1,2-a]-pyridin-7-yl]dimethylamine (**10**)*

A solution of imidate **8** (theoretically 490 mg, 1.30 mmol) was charged with EtOH (100 mL), then dimethylamine (26.0 mL of a 2.0 M solution in THF, 52.0 mmol) and heated

Table 4
Biological activity of 7-substituted imidazopyridines: 6-membered amine side chains



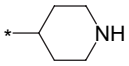
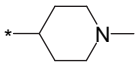
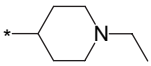
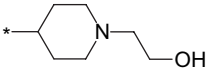
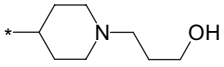
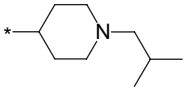
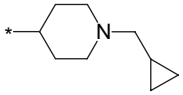
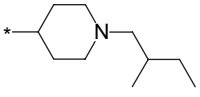
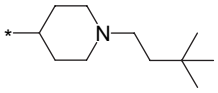
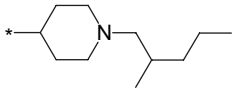
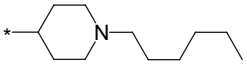
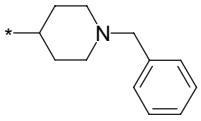
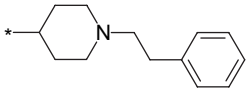
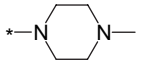
Compound	R	Ten_K IC_{50} (nM)	ExMAC dose (ppm)	ExMAC rating			
				E_t	E_a	E_{mi}	E_{ma}
68	$CH_2N(CH_3)_2$	0.11	25	3	3	3	3
			12.5	3	3	3	3
			6.25	3	3	0	0
61		0.046	25	0	0	0	4
69		0.044	25	4	4	4	4
			12.5	4	4	4	4
			10	4	4	4	4
			8	4	3	3	4
			6	4	3	3	4
62a		0.12	25	4	4	4	4
			12.5	4	3	4	4
			10	4	3	3	4
			8	4	3	3	4
			6	4	0	3	0
62b		0.044	25	3+	3+	0	2
			12.5	3+	2	3	3
			6.25	3+	0	0	0
62c		0.065	25	4	3	0	0
			12.5	4	0	0	0
			6.25	0	2	0	0
62d		0.12	25	4	4	4	4
			12.5	4	3	3	4
			6.25	2	3	0	3
62e		0.095	25	4	4	3	3
			12.5	4	3	3	3
			6.25	3	3	3	3
62f		0.13	12.5	3	3	0	
62g		0.11	12.5	3	0	0	

Table 4 (*continued*)

Compound	R	Ten_K IC_{50} (nM)	ExMAC dose (ppm)	ExMAC rating			
				E_t	E_a	E_{mi}	E_{ma}
62h		0.12	12.5	3	0	0	
62i		0.13	12.5	2	0	0	
62j		0.11	25	3	0	0	4
			12.5	3	3	0	3
			6.25	0	0	0	3
62k		0.07	12.5	0	0	0	
67		0.23	25	3	0	3	4
			12.5	3	0	2	0
			6.25	0	0	2	0

to 80 °C for 2 h. The reaction was then concentrated under reduced pressure, and then chromatographed on SiO_2 using a gradient that started with CH_2Cl_2 and ended with 90:9:1 CH_2Cl_2:MeOH:concentrated NH_4OH. Yield of **9**: 210 mg (43%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.10 (s, 6H), 5.17 (bs, 2H), 6.54 (d, $J = 5.3$ Hz, 1H), 6.98 (d, $J = 7.2$ Hz, 1H), 7.14 (t, $J = 8.7$ Hz, 2H), 7.61–7.69 (m, 2H), 7.73 (bs, 1H), 8.18 (d, $J = 5.3$ Hz, 1H), 9.55 (d, $J = 7.2$ Hz, 1H). Yield of **10**: 70 mg (20%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.49 (s, 6H), 5.21 (bs, 2H), 6.54 (d, $J = 5.3$ Hz, 1H), 7.15 (t, $J = 8.7$ Hz, 2H), 7.43 (d, $J = 7.4$ Hz, 1H), 7.61–7.69 (m, 2H), 8.10 (bs, 1H), 8.19 (d, $J = 5.3$ Hz, 1H), 9.50 (d, $J = 7.4$ Hz, 1H). MS (ESI+) 349.1.

*4.1.9. 2-(4-Fluorophenyl)-3-(2-methylsulfanylpyrimidin-4-yl)-imidazo[1,2-a]pyridine-7-carboxylic acid ethyl ester (**12**)*

A solution of bromide **11** (16.2 g, 47.5 mmol) in EtOH (100 mL) was charged with 2-(amino)isonicotinic acid ethyl ester (7.89 g, 47.5 mmol), then heated to 60 °C for 12 h, after which it was concentrated under reduced pressure, then triturated with EtOH, then filtered. The filter cake was rinsed with EtOH and then dried in a vacuum oven, yielding 7.79 g (40%) of imidazopyridine **12**. The remaining filtrate was then concentrated under reduced pressure and suspended in EtOH (100 mL), then charged with additional 2-(amino)isonicotinic acid ethyl ester (5.40 g, 32.5 mmol), and heated to 90 °C for 12 h, after which it was concentrated under reduced pressure, and then triturated with EtOH, and then filtered. The filter cake was rinsed with EtOH, and then dried in a vacuum oven, yielding an additional 7.11 g (36%) of imidazopyridine **12**. Total yield of **12**: 14.9 g (76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (t, $J = 7.2$ Hz, 3H), 2.65 (s, 3H), 4.45 (q, $J = 7.2$ Hz, 2H), 6.85 (d, $J = 5.0$ Hz, 1H), 7.15 (t, $J = 8.6$ Hz, 2H), 7.58 (d, $J = 7.4$ Hz, 1H), 7.60–7.68 (m, 2H), 8.36 (d, $J = 5.0$ Hz, 1H), 8.45 (bs, 1H), 9.55 (d, $J = 7.4$ Hz, 1H). MS (ESI+) 409.3.

*4.1.10. 2-(4-Fluorophenyl)-3-(2-methylsulfanylpyrimidin-4-yl)imidazo[1,2-a]pyridine-7-carboxylic acid methoxymethylamide (**13**)*

A solution of ester **12** (10.0 g, 24.5 mmol) in THF (200 mL) was charged with *N*,*O*-dimethylhydroxylamine hydrochloride (7.20 g, 73.4 mmol), then cooled to 0 °C in an ice water bath. The reaction was then charged with the dropwise addition of isopropylmagnesium chloride (73.5 mL of a 2.0 M solution in THF, 147 mmol), then allowed to warm to room temperature and stir for 12 h, after which it was quenched with saturated aqueous NH_4Cl solution (250 mL), then extracted with CH_2Cl_2 (2 × 250 mL). The organic fractions were pooled, dried over Na_2SO_4, filtered, and then chromatographed on SiO_2 using a gradient that started with heptane and ended with EtOAc. Yield of **13**: 5.60 g (54%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.68 (s, 3H), 3.45 (s, 3H), 3.66 (s, 3H), 6.87 (d, $J = 5.5$ Hz, 1H), 7.18 (t, $J = 8.5$ Hz, 2H), 7.37 (dd, $J = 7.5$, 2.0 Hz, 1H), 7.62–7.80 (m, 2H), 8.20

(bs, 1H), 8.36 (d, $J = 5.5$ Hz, 1H), 9.58 (d, $J = 7.5$ Hz, 1H). MS (ESI+) 424.2.

4.1.11. 2-(4-Fluorophenyl)-3-(2-methanesulfonylpyrimidin-4-yl)imidazo[1,2-a]pyridine-7-carboxylic acid methoxymethylamide (**14**)

A solution of sulfide **13** (2.00 g, 4.72 mmol) in 1:1 MeOH:acetone (100 mL) was charged with a solution of OXONE® (8.70 g, 14.2 mmol) in H_2O (50 mL). The reaction was stirred at room temperature for 12 h, and was then concentrated under reduced pressure to remove as much of the organic solvent as possible, then diluted with H_2O (100 mL) and filtered. The filter cake was dried in a vacuum oven at 60 °C for 3 h. Yield of **14**: 1.60 g (76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.43 (s, 3H), 3.44 (s, 3H), 3.64 (s, 3H), 7.22 (t, $J = 8.5$ Hz, 2H), 7.34 (d, $J = 5.6$ Hz, 1H), 7.48 (dd, $J = 7.4$, 1.5 Hz, 1H), 7.60–7.68 (m, 2H), 8.19 (bs, 1H), 8.58 (d, $J = 5.5$ Hz, 1H), 9.88 (d, $J = 7.4$ Hz, 1H). MS (ESI+) 456.3.

4.1.12. 3-(2-Aminopyrimidin-4-yl)-2-(4-fluorophenyl)-imidazo[1,2-a]pyridine-7-carboxylic acid methoxymethylamide (**15**)

A suspension of sulfone **14** (1.60 g, 3.51 mmol) in THF (100 mL) was chilled in a pressure reactor to −70 °C in a CO_2/IPA bath. Ammonia (16 g, 0.94 mol) was then bubbled in over 15 min, after which the pressure reactor was sealed, and the reaction was allowed to warm to room temperature with stirring for 12 h, during which the reaction pressure reached 65 psi. The pressure was then released, and the reaction was concentrated under reduced pressure, and then chromatographed on SiO_2 using a gradient that started with CH_2Cl_2 and ended with 90:9:1 CH_2Cl_2:MeOH:concentrated NH_4OH. Yield of **15**: 1.10 g (80%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.32 (s, 3H), 3.62 (s, 3H), 6.37 (d, $J = 5.2$ Hz, 1H), 6.90 (s, 2H), 7.22 (dd, $J = 7.3$, 1.6 Hz, 1H), 7.30 (t, $J = 8.8$ Hz, 2H), 7.65–7.73 (m, 2H), 7.96 (bs, 1H), 8.17 (d, $J = 5.2$ Hz, 1H), 9.52 (d, $J = 7.3$ Hz, 1H). MS (ESI+) 393.3.

4.1.13. 1-[3-(2-Aminopyrimidin-4-yl)-2-(4-fluorophenyl)-imidazo[1,2-a]pyridin-7-yl]propan-1-one (**16**) and 3-(2-aminopyrimidin-4-yl)-2-(4-fluorophenyl)imidazo-[1,2-a]pyridine-7-carboxylic acid methyl amide (**17**)

A suspension of Weinreb amide **15** (1.02 g, 2.60 mmol) in THF (175 mL) was charged with the dropwise addition of ethylmagnesium bromide (26.0 mL of a 1.0 M solution in THF, 26.0 mmol), and the reaction was stirred at room temperature for 12 h, after which a second portion of ethylmagnesium bromide (25.0 mL of a 1.0 M solution in THF, 25.0 mmol) was added. After stirring at room temperature for an additional 2 h, the reaction was quenched with saturated aqueous NH_4Cl solution (300 mL); the layers were separated, and the aqueous layer was back-extracted with CH_2Cl_2 (2 × 250 mL). The organic fractions were pooled, dried over Na_2SO_4, filtered, concentrated under reduced pressure, and then chromatographed on SiO_2 using a gradient that started with CH_2Cl_2 and ended with 90:9:1 CH_2Cl_2:MeOH:concentrated NH_4OH. Yield of **16**: 220 mg (23%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, $J = 7.2$ Hz, 3H), 3.07 (q, $J = 7.2$ Hz, 2H), 5.42 (bs, 2H), 6.50 (d, $J = 5.4$ Hz, 1H), 7.13 (t, $J = 8.6$ Hz, 2H), 7.49 (dd, $J = 7.4$, 1.5 Hz, 1H), 7.62 (m, 2H), 8.13 (d, $J = 5.4$ Hz, 1H), 8.26 (bs, 1H), 9.43 (d, $J = 7.4$ Hz, 1H). MS (ESI+) 362.3. Yield of **17**: 260 mg (28%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.99 (s, 3H), 5.51 (bs, 2H), 6.44 (d, $J = 5.4$ Hz, 1H), 7.12 (t, $J = 8.6$ Hz, 2H), 7.47 (dd, $J = 7.3$, 1.8 Hz, 1H), 7.54–7.60 (m, 2H), 7.99 (bs, 1H), 8.08 (d, $J = 5.4$ Hz, 1H), 9.47 (d, $J = 7.3$ Hz, 1H). MS (ESI+) 363.3.

4.1.14. 2-(4-Fluorophenyl)-3-(2-methylsulfanylpyrimidin-4-yl)imidazo[1,2-a]pyridine-7-carbaldehyde (**18**)

A solution of alcohol **1** (3.66 g, 9.99 mol) in CH_2Cl_2 (750 mL) was charged with manganese(IV) oxide (21.7 g, 250 mmol). The reaction was stirred at room temperature for 5 h, and was then filtered through Celite, and the Celite filter cake was then rinsed with CH_2Cl_2 (750 mL) and EtOAc (500 mL). The filtrate was then concentrated under reduced pressure and dried under vacuum, and not purified further. Yield of **18**: 2.39 g (66%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.65 (s, 3H), 6.87 (d, $J = 5.5$ Hz, 1H), 7.17 (t, $J = 9.0$ Hz, 2H), 7.51 (d, $J = 7.5$ Hz, 1H), 7.62–7.68 (m, 2H), 8.27 (bs, 1H), 8.40 (d, $J = 5.5$ Hz, 1H), 9.54 (d, $J = 7.5$ Hz, 1H), 10.08 (s, 1H). MS (ESI+) 365.2.

4.1.15. 1-[2-(4-Fluorophenyl)-3-(2-methanesulfanylpyrimidin-4-yl)imidazo[1,2-a]pyridin-7-yl]propan-1-one (**19**)

A solution of Weinreb amide **13** (5.60 g, 13.2 mmol) and THF (100 mL) was cooled to −70 °C in a CO_2/IPA bath, then charged with the dropwise addition of ethylmagnesium bromide (15 mL of a 1.0 M solution in THF, 15.0 mmol). Additional aliquots of ethylmagnesium bromide (15 mL of a 1.0 M solution in THF, 15.0 mmol) were added at $t = 2$ h and $t = 12$ h. After stirring for an additional 3 h, the reaction was then quenched with a saturated aqueous NH_4Cl solution (200 mL), and then extracted with CH_2Cl_2 (3 × 200 mL). The organic fractions were pooled, dried over Na_2SO_4, filtered, and concentrated under reduced pressure, and then chromatographed on SiO_2 using a gradient that started with CH_2Cl_2 and ended with 96:3.6:0.4 CH_2Cl_2:MeOH:concentrated NH_4OH. Yield of **19**: 1.50 g (29%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, $J = 7.3$ Hz, 3H), 2.65 (s, 3H), 3.08 (q, $J = 7.3$ Hz, 2H), 6.85 (d, $J = 5.2$ Hz, 1H), 7.15 (t, $J = 8.6$ Hz, 2H), 7.56 (d, $J = 7.2$ Hz, 1H), 7.59–7.67 (m, 2H), 8.30 (bs, 1H), 8.36 (d, $J = 5.2$ Hz, 1H), 9.53 (d, $J = 7.2$ Hz, 1H). MS (ESI+) 393.1.

4.1.16. 1-[2-(4-Fluorophenyl)-3-(2-methylsulfanylpyrimidin-4-yl)imidazo[1,2-a]pyridin-7-yl]ethanol (**20a**)

A solution of aldehyde **18** (1.00 g, 2.74 mmol) in THF (100 mL) was chilled to −70 °C in a CO_2/IPA bath, then charged with the dropwise addition of methylmagnesium bromide (7.35 mL of a 1.4 M in 3:1 toluene:THF, 10.3 mmol). After stirring at −70 °C for 2 h, the reaction was quenched

with H_2O (50 mL) and extracted into EtOAc (3 × 200 mL). The organic fractions were pooled, dried over Na_2SO_4, filtered, and concentrated under reduced pressure, and then chromatographed on SiO_2 using a gradient that started with CH_2Cl_2 and ended with 97:2.7:0.3 CH_2Cl_2:MeOH:concentrated NH_4OH. Yield of **20a**: 600 mg (58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.56 (d, $J = 6.4$ Hz, 3H), 2.70 (s, 3H), 4.97 (q, $J = 6.4$ Hz, 1H), 6.83 (d, $J = 5.5$ Hz, 1H), 7.03 (dd, $J = 7.3$, 1.5 Hz, 1H), 7.20 (t, $J = 8.7$ Hz, 2H), 7.61–7.69 (m, 2H), 7.73 (bs, 1H), 8.34 (d, $J = 5.5$ Hz, 1H), 9.52 (d, $J = 7.3$ Hz, 1H). MS (ESI+) 380.9.

*4.1.17. 1-[2-(4-Fluorophenyl)-3-(2-methanesulfanylpyrimidin-4-yl)imidazo[1,2-a]pyridin-7-yl]propan-1-ol (**20b**)*

A solution of ketone **19** (1.50 g, 3.82 mmol) in EtOH (100 mL) was charged with $NaBH_4$ (174 mg, 4.60 mmol), and the reaction was allowed to stir at room temperature for 12 h, and was then quenched with a saturated aqueous $NaHCO_3$ solution (150 mL) then extracted into CH_2Cl_2 (2 × 100 mL). The organic fractions were pooled, dried over Na_2SO_4, filtered, and concentrated under reduced pressure, and not purified further. Yield of **20b**: 1.52 g (100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, $J = 7.4$ Hz, 3H), 1.78 (m, 2H), 2.58 (s, 3H), 4.62–4.70 (m, 1H), 6.74 (d, $J = 5.4$ Hz, 1H), 6.95 (d, $J = 7.4$ Hz, 1H), 7.07 (t, $J = 8.6$ Hz, 2H), 7.55 (m, 2H), 7.58 (bs, 1H), 8.22 (d, $J = 5.4$ Hz, 1H), 9.49 (d, $J = 7.4$ Hz, 1H). MS (ESI+) 395.2.

*4.1.18. General procedure for the synthesis of mesylates **21a** and **21b***

A solution of appropriate alcohol in THF was cooled to 0 °C in an ice water bath, charged with Et_3N and methanesulfonyl chloride, and then allowed to warm to room temperature with stirring for 12 h. The reaction was cooled again to 0 °C and charged with additional portions of both Et_3N and methanesulfonyl chloride as indicated, and allowed to warm to room temperature again. Once starting material was consumed, the product was then either isolated by aqueous workup (EtOAc, H_2O), or carried directly onto the next step in the same reaction vessel.

*4.1.18.1. Methanesulfonic acid 1-[2-(4-fluorophenyl)-3-(2-methylsulfanylpyrimidin-4-yl)imidazo[1,2-a]pyridin-7-yl]ethyl ester (**21a**).*

Mesylate **21a** was prepared from alcohol **20a** (1.00 g, 2.64 mmol), Et_3N (801 mg, 7.92 mmol at $t = 0$ h and $t = 12$ h), and methanesulfonyl chloride (663 mg, 5.81 mmol at $t = 0$ h and $t = 12$ h) in THF (20 mL). After stirring for 5 h beyond the second addition of reagents, the reaction was then quenched with saturated aqueous $NaHCO_3$ solution (100 mL), and extracted into EtOAc (2 × 50 mL). The organic fractions were pooled, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Crude mesylate **21a** was then carried directly onto the next step. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.78 (d, $J = 6.6$ Hz, 3H), 2.65 (s, 3H), 2.97 (s, 3H), 5.84 (q, $J = 6.6$ Hz, 1H), 6.83 (d, $J = 5.4$ Hz, 1H), 7.06 (dd, $J = 7.4$, 1.6 Hz, 1H), 7.16 (t, $J = 8.6$ Hz, 2H), 7.59–7.67 (m, 2H), 7.75 (bs, 1H), 8.33 (d, $J = 5.4$ Hz, 1H), 9.62 (d, $J = 7.4$ Hz, 1H). MS (ESI+) 394.9 (resulting from displacement of $-OSO_2CH_3$ by $-OCH_3$ in the MS).

*4.1.18.2. Methanesulfonic acid 1-[2-(4-fluorophenyl)-3-(2-methylsulfanylpyrimidin-4-yl)imidazo[1,2-a]pyridin-7-yl]propyl ester (**21b**).*

Mesylate **21b** was prepared from alcohol **20b** (1.52 g, 3.82 mmol), Et_3N (1.16 g, 11.5 mmol at $t = 0$ h and $t = 12$ h), and methanesulfonyl chloride (0.960 g, 8.40 mmol at $t = 0$ h and $t = 12$ h) in THF (100 mL). After stirring for 12 h beyond the second addition of reagents, the reaction was carried onto the next step (synthesis of dimethylamine **22b**) in the same reaction vessel without prior isolation of the mesylate.

*4.1.19. General procedure for the synthesis of tertiary amines **22a** and **22b***

A solution of appropriate mesylate in THF was charged with dimethylamine (2.0 M solution in THF), with additional portions added as indicated. The reaction was then quenched with water and extracted into EtOAc, dried over Na_2SO_4, filtered, concentrated under reduced pressure, and chromatographed on SiO_2 using a gradient that started with CH_2Cl_2 and ended with 90:9:1 CH_2Cl_2:MeOH:concentrated NH_4OH.

*4.1.19.1. {1-[2-(4-Fluorophenyl)-3-(2-methylsulfanylpyrimidin-4-yl)imidazo[1,2-a]pyridin-7-yl]ethyl}dimethylamine (**22a**).*

Dimethylamine **22a** was prepared from mesylate **21a** (theoretically 422 mg, 0.920 mmol) and dimethylamine (920 μL of a 2.0 M solution in THF, 1.84 mmol at $t = 0$ h, $t = 2$ h, and $t = 4$ h) in THF (10 mL). After stirring for 12 h beyond the final addition of dimethylamine solution, the reaction was worked up and chromatographed as described in the general procedure above. Yield of **22a**: 110 mg (30% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (d, $J = 6.7$ Hz, 3H), 2.25 (s, 6H), 2.63 (s, 3H), 3.38 (q, $J = 6.7$ Hz, 1H), 6.80 (d, $J = 5.4$ Hz, 1H), 7.09 (dd, $J = 7.4$, 1.5 Hz, 1H), 7.13 (t, $J = 8.7$ Hz, 2H), 7.56 (bs, 1H), 7.57–7.65 (m, 2H), 8.27 (d, $J = 5.4$ Hz, 1H), 9.54 (d, $J = 7.4$ Hz, 1H). MS (ESI+) 407.6.

*4.1.19.2. {1-[2-(4-Fluorophenyl)-3-(2-methylsulfanylpyrimidin-4-yl)imidazo[1,2-a]pyridin-7-yl]propyl}dimethylamine (**22b**).*

Dimethylamine **22b** was prepared from mesylate **21b** (theoretically 1.81 g, 3.82 mmol) and dimethylamine (19.1 mL of a 2.0 M solution in THF, 38.2 mmol at $t = 0$ h and $t = 12$ h) in THF (100 mL). After stirring for 72 h beyond the final addition of dimethylamine solution, the reaction was worked up and chromatographed as described in the general procedure above. Yield of **22b**: 800 mg (50% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.77 (t, $J = 7.2$ Hz, 3H), 1.69–1.77 (m, 1H), 1.93–2.01 (m, 1H), 2.23 (s, 6H), 2.63 (s, 3H), 3.12 (dd, $J = 5.6$, 0.8 Hz, 1H), 6.80 (d, $J = 5.2$ Hz, 1H), 6.98 (dd, $J = 7.2$, 2.0 Hz, 1H), 7.08–7.16 (m, 2H), 7.50 (bs, 1H),

7.57–7.65 (m, 2H), 8.26 (d, $J = 5.2$ Hz, 1H), 9.53 (d, $J = 7.2$ Hz, 1H). MS (ESI+) 422.1.

4.1.20. {1-[2-(4-Fluorophenyl)-3-(2-methanesulfonylpyrimidin-4-yl)imidazo[1,2-a]pyridin-7-yl]ethyl}-dimethylamine (**23a**)

A solution of sulfide **22a** (625 mg, 1.35 mmol) in MeOH (25 mL) was charged with AcOH (919 mg, 876 μL, 15.3 mmol), hydrogen peroxide (730 mg of a 30% w/w aqueous solution, 658 μL, 6.43 mmol), and sodium tungstate dihydrate (152 mg, 0.461 mmol). After stirring for 4 h at room temperature, second portions of AcOH (919 mg, 876 μL, 15.3 mmol) and hydrogen peroxide (730 mg of a 30% w/w aqueous solution, 658 μL, 6.43 mmol) were added, and stirring continued at room temperature for 12 h. The reaction was then cooled to −70 °C in a CO_2/IPA bath, and charged with sulfur dioxide (22 g). The reaction was stirred at below −20 °C for 3 h, and then allowed to warm to room temperature, and was then quenched with a saturated aqueous $NaHCO_3$ solution (250 mL), and extracted into EtOAc (3 × 100 mL). The organic fractions were pooled, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Crude sulfone **23a** was then carried onto the next step without further purification. MS (ESI+) 394.9 (resulting from displacement of $-N(CH_3)_2$ by $-OCH_3$ in the MS).

4.1.21. {1-[2-(4-Fluorophenyl)-3-(2-methanesulfonylpyrimidin-4-yl)imidazo[1,2-a]pyridin-7-yl]propyl}-dimethylamine (**23b**)

A solution of sulfide **22b** (800 mg, 1.90 mmol) was charged with MeOH (25 mL), then a solution of OXONE® (3.5 g, 5.7 mmol) in H_2O (25 mL), then acetone (25 mL), and the reaction was allowed to stir at room temperature for 12 h. The reaction was then cooled to −50 °C in a CO_2/IPA bath, and charged with sulfur dioxide gas (6.6 g). The reaction was then allowed to warm to room temperature for 3 h, after which it was neutralized with a saturated aqueous $NaHCO_3$ solution, and extracted into CH_2Cl_2 (2 × 250 mL). The organic extracts were pooled, dried over Na_2SO_4, filtered, and concentrated under reduced pressure, and carried onto the next step without further purification. Crude yield of **23b**: 886 mg (100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.73 (t, $J = 7.2$ Hz, 3H), 1.69–1.74 (m, 1H), 1.89–1.95 (m, 1H), 2.19 (s, 6H), 3.09–3.17 (m, 1H), 3.33 (s, 3H), 7.06 (d, $J = 7.2$ Hz, 1H), 7.14 (t, $J = 8.4$ Hz, 2H), 7.21 (d, $J = 5.6$ Hz, 1H), 7.51 (bs, 1H), 7.52–7.60 (m, 2H), 8.43 (d, $J = 5.6$ Hz, 1H), 9.79 (d, $J = 7.2$ Hz, 1H). MS (ESI+) 454.2.

4.1.22. General procedure for the synthesis of 2-aminopyrimidines **24a** and **24b**

A suspension of appropriate sulfone in THF was chilled in a pressure reactor to −60 °C to −70 °C in a CO_2/IPA bath, and charged with excess ammonia gas. The pressure reactor was sealed, and the reaction was allowed to warm to room temperature with stirring for 12 h, during which the reaction pressure had reached 35–50 psi. The pressure was then released, and the reaction was concentrated under reduced pressure, and then chromatographed on SiO_2 using a gradient that started with CH_2Cl_2 and ended with 90:9:1 CH_2Cl_2:MeOH:concentrated NH_4OH.

4.1.22.1. 4-[7-(1-Dimethylaminoethyl)-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-ylamine (**24a**).

2-Aminopyrimidine **24a** was prepared from sulfone **23a** (theoretically 672 mg, 1.53 mmol) and ammonia (3.50 g, 205 mmol) in THF (50 mL). Yield of **24a**: 240 mg (42% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (d, $J = 6.6$ Hz, 3H), 2.26 (s, 6H), 3.37 (q, $J = 6.6$ Hz, 1H), 5.23 (bs, 2H), 6.51 (d, $J = 5.4$ Hz, 1H), 7.03 (dd, $J = 7.3$, 1.3 Hz, 1H), 7.11 (t, $J = 8.7$ Hz, 2H), 7.54 (bs, 1H), 7.60–7.68 (m, 2H), 8.11 (d, $J = 5.4$ Hz, 1H), 9.41 (d, $J = 7.3$ Hz, 1H). MS (ESI+) 376.8. The two enantiomers of **24a** were then separated on a ChiralCel OJ column (Diacel) by eluting with 15% isopropyl alcohol and 85% heptane.

4.1.22.2. 4-[7-(1-Dimethylaminopropyl)-2-(4-fluorophenyl)-imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-ylamine (**24b**).

2-Aminopyrimidine **24b** was prepared from sulfone **23b** (theoretical quantity: 862 mg, 1.90 mmol) and ammonia (13.4 g, 787 mmol) in THF (50 mL). Yield of **24b**: 500 mg (68% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.77 (t, $J = 7.2$ Hz, 3H), 1.70–1.77 (m, 1H), 1.93–2.00 (m, 1H), 2.24 (s, 6H), 3.11 (dd, $J = 5.6$, 4.4 Hz, 1H), 5.12 (bs, 2H), 6.52 (d, $J = 5.6$ Hz, 1H), 6.93 (dd, $J = 7.5$, 1.4 Hz, 1H), 7.07–7.15 (m, 2H), 7.48 (bs, 1H), 7.59–7.67 (m, 2H), 8.11 (d, $J = 5.6$ Hz, 1H), 9.41 (d, $J = 7.5$ Hz, 1H). MS (ESI+) 391.3.

4.1.23. [2-(4-Fluorophenyl)-3-(2-methylsulfanylpyrimidin-4-yl)imidazo[1,2-a]pyridin-7-yl]acetonitrile (**26**)

A solution of mesylate **25** (7.40 g, 16.6 mmol) in CH_2Cl_2 (200 mL) was charged with tetra-*n*-butylammonium cyanide (4.47 g, 16.6 mmol). After stirring at room temperature for 12 h, the reaction was concentrated under reduced pressure, and then chromatographed on SiO_2 using a gradient that started with heptane and ended with EtOAc. Yield of **26**: 4.20 g (67%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.65 (s, 3H), 3.88 (s, 2H), 6.83 (d, $J = 5.2$ Hz, 1H), 6.95 (dd, $J = 7.5$, 2.0 Hz, 1H), 7.15 (t, $J = 8.8$ Hz, 2H), 7.58–7.66 (m, 2H), 7.69 (bs, 1H), 8.32 (d, $J = 5.2$ Hz, 1H), 9.61 (d, $J = 7.5$ Hz, 1H). MS (ESI+) 376.2.

4.1.24. General procedure for the synthesis of α-alkylated nitriles **27a** and **27b**

A solution of nitrile **26** in THF was cooled to 0 °C in an ice water bath, and then charged with NaH in portions. After stirring for 5 min, appropriate alkyl halide was added. After warming to room temperature and stirring for the indicated length of time, then reaction was worked up (EtOAc, H_2O), dried over Na_2SO_4, filtered, concentrated under reduced pressure, and chromatographed on SiO_2 using a gradient that started with heptane and ended with 50:50 EtOAc:heptane.

4.1.24.1. 2-[2-(4-Fluorophenyl)-3-(2-methylsulfanylpyrimidin-4-yl)imidazo[1,2-a]pyridin-7-yl]pentanenitrile (**27a**).

α-*n*-Propylnitrile **27a** was prepared from nitrile **26** (3.00 g, 7.99 mmol), NaH (352 mg of a 60% w/w suspension in

mineral oil, 8.79 mmol), and 1-bromopropane (2.95 g, 2.18 mL, 24.0 mmol) in THF (100 mL) with 12 h of stirring. Yield of **27a**: 1.77 g (53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (t, $J = 7.3$ Hz, 3H), 1.49–1.65 (m, 2H), 1.88–2.09 (m, 2H), 2.66 (s, 3H), 3.93 (dd, $J = 8.0$, 6.4 Hz, 1H), 6.84 (d, $J = 5.5$ Hz, 1H), 6.99 (dd, $J = 7.2$, 1.9 Hz, 1H), 7.16 (t, $J = 8.6$ Hz, 2H), 7.59–7.67 (m, 2H), 7.68 (bs, 1H), 8.33 (d, $J = 5.5$ Hz, 1H), 9.63 (d, $J = 7.2$ Hz, 1H). MS (ESI+) 418.1.

*4.1.24.2. 2-[2-(4-Fluorophenyl)-3-(2-methylsulfanylpyrimidin-4-yl)imidazo[1,2-a]pyridin-7-yl]-2-methylpropiontirile (**27b**).* α,α-Dimethylnitrile **27b** was prepared from nitrile **26** (3.70 g, 9.85 mmol), NaH (1.18 g of 60% w/w suspension in mineral oil, 29.6 mmol), and methyl iodide (3.08 g, 21.7 mmol) in THF (200 mL) with 30 min of stirring. Yield of **27b**: 3.21 g (81%). ^{1}H NMR 400 MHz, $CDCl_3$) δ 1.80 (s, 6H), 2.64 (s, 3H), 6.82 (d, $J = 5.6$ Hz, 1H), 7.11 (d, $J = 7.3$ Hz, 1H), 7.14 (t, $J = 8.6$ Hz, 2H), 7.57–7.65 (m, 2H), 7.77 (bs, 1H), 8.31 (d, $J = 5.6$ Hz, 1H), 9.61 (d, $J = 7.3$ Hz, 1H). MS (ESI+) 404.2.

*4.1.25. General procedure for the synthesis of amides **28a** and **28b***

Appropriate nitrile was chilled in an ice water bath and treated with the dropwise addition of concentrated H_2SO_4. The reaction was then heated to 100 °C for 3 h, cooled to room temperature, and then neutralized by the slow addition of saturated aqueous $NaHCO_3$ solution until basic to litmus paper. The mixture was then extracted into EtOAc. The organic fractions were pooled, dried over Na_2SO_4, filtered, and concentrated under reduced pressure, and not purified further.

*4.1.25.1. 2-[2-(4-Fluorophenyl)-3-(2-methylsulfanylpyrimidin-4-yl)imidazo[1,2-a]pyridin-7-yl]pentanoic acid amide (**28a**).* Amide **28a** was prepared from nitrile **27a** (1.67 g, 4.00 mmol) and concentrated H_2SO_4 (20 mL). Yield of **28a**: 1.48 g (85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (t, $J = 7.3$ Hz, 3H), 1.29–1.42 (m, 2H), 1.78–1.89 (m, 1H), 2.08–2.19 (m, 1H), 2.65 (s, 3H), 3.51 (t, $J = 7.6$ Hz, 1H), 5.53 (bs, 1H), 5.79 (bs, 1H), 6.80 (d, $J = 5.4$ Hz, 1H), 7.08 (dd, $J = 7.2$, 1.7 Hz, 1H), 7.15 (t, $J = 8.7$ Hz, 2H), 7.59 (bs, 1H), 7.59–7.66 (m, 2H), 8.30 (d, $J = 5.4$ Hz, 1H), 9.56 (d, $J = 7.2$ Hz, 1H). MS (ESI+) 436.2.

*4.1.25.2. 2-[2-(4-Fluorophenyl)-3-(2-methylsulfanylpyrimidin-4-yl)imidazo[1,2-a]pyridin-7-yl]isobutyramide (**28b**).* Amide **28b** was prepared from nitrile **27b** (1.85 g, 4.59 mmol) and concentrated H_2SO_4 (20 mL). Yield of **28b**: 1.87 g (96%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.68 (s, 6H), 2.66 (s, 3H), 5.40 (m, 2H), 6.83 (d, $J = 5.2$ Hz, 1H), 7.00 (d, $J = 7.5$ Hz, 1H), 7.17 (t, $J = 8.8$ Hz, 2H), 7.60–7.68 (m, 2H), 7.74 (bs, 1H), 8.32 (d, $J = 5.2$ Hz, 1H), 9.54 (d, $J = 7.5$ Hz, 1H). MS (ESI+) 422.2.

*4.1.26. General procedure for the synthesis of primary amines **29a** and **29b***

A solution of appropriate amide in CH_3CN was charged with bis(trifluoroacetoxy)iodobenzene in portions, and allowed to stir at room temperature for 12 h. The reaction was then treated with the dropwise addition of concentrated HCl and allowed to stir at room temperature for 15 min, after which it was treated with 2 N NaOH solution until it became basic to litmus paper. The mixture was then extracted repeatedly into EtOAc. The organic fractions were pooled, washed with H_2O (2 × 100 mL), dried over Na_2SO_4, filtered, concentrated under reduced pressure, and then chromatographed on SiO_2 using a gradient that started with CH_2Cl_2 and ended with 90:9:1 CH_2Cl_2:MeOH:concentrated NH_4OH.

*4.1.26.1. 1-[2-(4-Fluorophenyl)-3-(2-methylsulfanylpyrimidin-4-yl)imidazo[1,2-a]pyridin-7-yl]butylamine (**29a**).* Amine **29a** was prepared from amide **28a** (460 mg, 1.05 mmol) and bis-(trifluoroacetoxy)iodobenzene (454 mg, 1.05 mmol) in CH_3CN (10 mL). Yield of **29a**: 110 mg (26%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (t, $J = 7.3$ Hz, 3H), 1.23–1.46 (m, 2H), 1.70 (q, $J = 7.4$ Hz, 2H), 2.65 (s, 3H), 4.03 (t, $J = 6.8$ Hz, 1H), 6.81 (d, $J = 5.4$ Hz, 1H), 7.03 (dd, $J = 7.3$, 1.6 Hz, 1H), 7.14 (t, $J = 8.6$ Hz, 2H), 7.61 (bs, 1H), 7.59–7.67 (m, 2H), 8.28 (d, $J = 5.4$ Hz, 1H), 9.56 (d, $J = 7.3$ Hz, 1H). MS (ESI+) 408.2.

*4.1.26.2. 1-[2-(4-Fluorophenyl)-3-(2-methylsulfanylpyrimidin-4-yl)imidazo[1,2-a]pyridin-7-yl]-1-methylethylamine (**29b**).* Amine **29b** was prepared from amide **28b** (400 mg, 0.949 mmol) and bis(trifluoroacetoxy)iodobenzene (410 mg, 0.953 mmol) in CH_3CN (40 mL). Yield of **29b**: 202 mg (54%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.65 (s, 6H), 2.66 (s, 3H), 6.82 (d, $J = 5.5$ Hz, 1H), 7.15 (t, $J = 8.8$ Hz, 2H), 7.20 (d, $J = 6.0$ Hz, 1H), 7.57–7.65 (m, 2H), 7.89 (bs, 1H), 8.30 (d, $J = 5.5$ Hz, 1H), 9.52 (d, $J = 7.5$ Hz, 1H). MS (ESI+) 394.2.

*4.1.27. General procedure for the synthesis of dimethylamines **30a** and **30b***

A solution of appropriate primary amine in CH_3OH was charged with formaldehyde, AcOH, and sodium cyanoborohydride. After stirring at room temperature for 3 h, the reaction was worked up (EtOAc, saturated $NaHCO_3$ solution), dried over Na_2SO_4, filtered, concentrated under reduced pressure, and then chromatographed on SiO_2 using a gradient that started with CH_2Cl_2 and ended with 90:9:1 CH_2Cl_2:MeOH:-concentrated NH_4OH.

*4.1.27.1. {1-[2-(4-Fluorophenyl)-3-(2-methylsulfanylpyrimidin-4-yl)imidazo[1,2-a]pyridin-7-yl]butyl}dimethylamine (**30a**).* Dimethylamine **30a** was prepared from primary amine **29a** (240 mg, 0.589 mmol), formaldehyde (143 mg of 37% w/w solution in H_2O, 131 μL), AcOH (240 μL), and sodium cyanoborohydride (2.94 mL of a 1.0 M solution in THF, 2.94 mmol) in CH_3OH (5.0 mL). Crude yield of **30a**: 310 mg (>100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, $J = 7.3$ Hz, 3H), 1.13–1.34 (m, 2H), 2.10 (s, 3H), 2.17 (q, $J = 7.7$ Hz, 1H), 2.67 (s, 3H), 2.79 (s, 3H), 3.50 (s, 1H), 4.08 (dd, $J = 9.1$, 6.4 Hz, 1H), 6.83 (d, $J = 5.4$ Hz, 1H), 7.17 (dd, $J = 7.2$, 2.0 Hz, 1H), 7.17 (t, $J = 8.6$ Hz, 2H), 7.57–7.65 (m, 2H), 7.77 (bs, 1H),

8.37 (d, $J = 5.4$ Hz, 1H), 9.69 (d, $J = 7.2$ Hz, 1H). MS (ESI+) 436.7.

*4.1.27.2. {1-[2-(4-Fluorophenyl)-3-(2-methylsulfanylpyrimidin-4-yl)imidazo[1,2-a]pyridin-7-yl]-1-methylethyl}dimethylamine (**30b**).* Dimethylamine **30b** was prepared from amine **29b** (643 mg, 1.63 mmol), formaldehyde (398 mg of a 37% w/w aqueous solution, 4.90 mmol), AcOH (3.1 mL), and sodium cyanoborohydride (8.17 mL of a 1.0 M solution in THF, 8.17 mmol) in MeOH (36 mL). Yield of **30b**: 560 mg (82%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.80 (bs, 6H), 2.65 (bs, 6H), 2.70 (s, 3H), 6.85 (d, $J = 5.5$ Hz, 1H), 7.18 (t, $J = 8.5$ Hz, 2H), 7.48 (d, $J = 7.5$ Hz, 1H), 7.60–7.68 (m, 2H), 7.78 (bs, 1H), 8.37 (bs, 1H), 9.67 (d, $J = 7.5$ Hz, 1H). MS (ESI+) 422.2.

*4.1.28. General procedure for the synthesis of sulfones **31a** and **31b***

A solution of appropriate sulfide in 1:1 MeOH:acetone was charged with a solution of OXONE® in H_2O, and allowed to stir at room temperature for 12 h. The reaction was then chilled to −40 °C in a CO_2/IPA bath. Excess sulfur dioxide gas was then bubbled in over 5 min. After stirring at −40 °C for an additional 15 min, the reaction was quenched with a saturated aqueous $NaHCO_3$ solution until basic to litmus paper, and then extracted repeatedly into EtOAc. The organic fractions were pooled, dried over Na_2SO_4, filtered, and concentrated under reduced pressure.

*4.1.28.1. {1-[2-(4-Fluorophenyl)-3-(2-methanesulfonylpyrimidin-4-yl)imidazo[1,2-a]pyridin-7-yl]butyl}dimethylamine (**31a**).* Sulfone **31a** was prepared from crude sulfide **30a** (theoretically 257 mg, 0.589 mmol) and OXONE® (1.08 g, 1.77 mol dissolved in 10 mL H_2O) in 1:1 MeOH:acetone (20 mL), and subsequent treatment with sulfur dioxide (12.9 g, 201 mmol). Yield of **31a**: 234 mg (85% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, $J = 7.2$ Hz, 3H), 1.10–1.25 (m, 2H), 1.68–1.82 (m, 1H), 1.87–1.98 (m, 1H), 2.26 (s, 6H), 3.26–3.36 (m, 1H), 3.41 (s, 3H), 7.15 (dd, $J = 7.2$, 1.7 Hz, 1H), 7.21 (t, $J = 8.8$ Hz, 2H), 7.29 (d, $J = 5.7$ Hz, 1H), 7.57 (bs, 1H), 7.60–7.67 (m, 2H), 8.51 (d, $J = 5.7$ Hz, 1H), 9.87 (d, $J = 7.2$ Hz, 1H). MS (ESI+) 468.0.

*4.1.28.2. {1-[2-(4-Fluorophenyl)-3-(2-methanesulfonylpyrimidin-4-yl)imidazo[1,2-a]pyridin-7-yl]-1-methylethyl}dimethylamine (**31b**).* Sulfone **31a** was prepared from sulfide **30b** (560 mg, 1.33 mmol) and OXONE® (2.45 g, 3.99 mmol dissolved in 20 mL H_2O) in 1:1 MeOH:acetone (50 mL), and subsequent treatment with sulfur dioxide (43 g, 670 mmol). Yield of **31b**: 354 mg (58%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.41 (bs, 6H), 2.25 (bs, 6H), 3.42 (s, 3H), 7.22 (t, $J = 8.5$ Hz, 2H), 7.30 (d, $J = 5.5$ Hz, 1H), 7.55 (bs, 1H), 7.61–7.68 (m, 2H), 7.77 (bs, 1H), 8.52 (d, $J = 5.0$ Hz, 1H), 9.83 (d, $J = 7.5$ Hz, 1H). MS (ESI+) 454.3.

*4.1.29. General procedure for the synthesis of 2-aminopyrimidines **32a** and **32b***

A suspension of appropriate sulfone in THF was chilled in a pressure reactor to −60 °C to −70 °C in a CO_2/IPA bath, and charged with excess ammonia gas. The pressure reactor was sealed, and the reaction was allowed to warm to room temperature with stirring for 12 h, during which the reaction pressure had reached 35–50 psi. The pressure was then released, and the reaction was concentrated under reduced pressure, and then chromatographed on SiO_2 using a gradient that started with CH_2Cl_2 and ended with 90:9:1 CH_2Cl_2:MeOH:concentrated NH_4OH.

*4.1.29.1. 4-[7-(1-Dimethylaminobutyl)-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-ylamine (**32a**).* 2-Aminopyridimine **32a** was prepared from sulfone **31a** (224 mg, 0.479 mmol) and ammonia (12.9 g, 757 mmol) in THF (20 mL). Yield of **32a**: 125 mg (64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, $J = 7.3$ Hz, 3H), 1.09–1.27 (m, 2H), 1.65–1.79 (m, 1H), 1.85–1.97 (m, 1H), 2.25 (s, 6H), 3.22 (dd, $J = 9.7$, 4.6 Hz, 1H), 5.13 (bs, 2H), 6.54 (d, $J = 5.4$ Hz, 1H), 6.94 (dd, $J = 7.2$, 1.7 Hz, 1H), 7.13 (t, $J = 8.8$ Hz, 2H), 7.50 (bs, 1H), 7.62–7.70 (m, 2H), 8.13 (d, $J = 5.4$ Hz, 1H), 9.43 (d, $J = 7.2$ Hz, 1H). MS (ESI+) 405.2.

*4.1.29.2. 4-[7-(1-Dimethylamino-1-methyl-ethyl)-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-ylamine (**32b**).* 2-Aminopyrimidine **32b** was prepared from sulfone **31b** (354 mg, 0.780 mmol) and ammonia (28.0 g, 1.64 mmol) in THF (150 mL). Yield of **32b**: 168 mg (55%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.40 (bs, 6H), 2.23 (bs, 6H), 5.11 (bs, 2H), 6.54 (d, $J = 5.5$ Hz, 1H), 7.14 (t, $J = 8.8$ Hz, 2H), 7.32 (d, $J = 6.8$ Hz, 1H), 7.62–7.69 (m, 3H), 8.14 (d, $J = 5.5$ Hz, 1H), 9.39 (d, $J = 6.8$ Hz, 1H). MS (ESI+) 391.2.

*4.1.30. 2-[2-(4-Fluorophenyl)-3-(2-methylsulfanylpyrimidin-4-yl)imidazo[1,2-a]pyridin-7-yl]propan-2-ol (**33**)*

A solution of ester **12** (327 mg, 0.828 mmol) in THF (30 mL) was chilled to 0 °C in an ice water bath, then charged with methylmagnesium bromide (2.96 mL of a 1.4 M solution in 3:1 toluene:THF, 4.14 mmol), and the reaction was allowed to warm to room temperature and stir for 12 h, after which a second portion of methylmagnesium bromide (2.96 mL of a 1.4 M solution in 3:1 toluene:THF, 4.14 mmol) was added. After stirring at room temperature for another 3 h, the reaction was concentrated under reduced pressure, diluted with CH_2Cl_2 (800 mL), and then washed with H_2O (3 × 100 mL). The organic layer was dried with Na_2SO_4, filtered, and concentrated under reduced pressure, and not purified further. Yield of **33**: 315 mg (96%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.50 (s, 6H), 2.60 (s, 3H), 6.88 (d, $J = 5.4$ Hz, 1H), 7.23–7.30 (m, 1H), 7.32 (t, $J = 8.6$ Hz, 2H), 7.62–7.70 (m, 2H), 7.73 (bs, 1H), 8.47 (d, $J = 5.4$ Hz, 1H), 9.36 (d, $J = 7.4$ Hz, 1H). MS (ESI+) 394.9.

*4.1.31. 2-[2-(4-Fluorophenyl)-3-(2-methanesulfonylpyrimidin-4-yl)imidazo[1,2-a]pyridin-7-yl]propan-2-ol (**34**)*

A solution of sulfide **33** (1.45 g, 3.68 mmol) in MeOH/acetone (7 mL + 56 mL) was charged with a solution of OXONE® (6.78 g, 11.0 mmol) in H_2O (60 mL). The reaction

was allowed to stir at room temperature for 12 h, and was then concentrated under reduced pressure to remove as much organic solvent as possible, then diluted with H_2O (200 mL), and extracted into EtOAc (4 × 50 mL). The organic fractions were pooled, washed with H_2O (2 × 50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Yield of **34**: 1.12 g (72%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.51 (s, 6H), 3.48 (s, 3H), 7.28–7.41 (m, 4H), 7.67–7.75 (m, 2H), 7.79 (bs, 1H), 8.80 (d, $J = 5.6$ Hz, 1H), 9.52 (d, $J = 7.4$ Hz, 1H). MS (ESI+) 426.9.

*4.1.32. 2-[3-(2-Aminopyrimidin-4-yl)-2-(4-fluorophenyl)-imidazo[1,2-a]pyridin-7-yl]propan-2-ol (**35**)*

A suspension of sulfone **34** (237 mg, 0.555 mmol) in THF (60 mL) in a pressure reactor was chilled to −78 °C in a CO_2/IPA bath, and ammonia (24.5 g, 144 mmol) was bubbled in over 15 min. The pressure reactor was sealed, and the reaction was allowed to warm to room temperature with stirring for 12 h, during which the reaction pressure reached 50 psi. The pressure was then released, and the reaction was concentrated under reduced pressure, and was then chromatographed on SiO_2 using a gradient that started with CH_2Cl_2 and ended with 90:9:1 CH_2Cl_2:MeOH:concentrated NH_4OH. Yield of **35**: 158 mg (78%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.50 (s, 6H), 6.32 (d, $J = 5.3$ Hz, 1H), 6.83 (s, 2H), 7.16 (dd, $J = 7.4$, 1.8 Hz, 1H), 7.29 (t, $J = 8.8$ Hz, 2H), 7.56–7.73 (m, 3H), 8.11 (d, $J = 5.3$ Hz, 1H), 9.47 (d, $J = 7.4$ Hz, 1H). MS (ESI+) 363.9.

*4.1.33. 4-[7-(1-Amino-1-methyl-ethyl)-2-(4-fluorophenyl)-imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-ylamine (**37**)*

A mixture of alcohol **35** (440 mg, 1.21 mmol) and NaCN (2.73 g, 55.9 mmol) was chilled to 0 °C in an ice water bath, then charged with the slow addition of AcOH (5.39 mL, 94.5 mmol), then allowed to stir for 10 min. A mixture of concentrated H_2SO_4 (3.4 mL, 63 mmol) in AcOH (1.00 mL, 17.2 mmol) was then added, and the reaction was allowed to warm to room temperature and stir for 1 h. The reaction was then heated to 70 °C for 2 h, then 90 °C for 2 h. The reaction was then diluted with EtOAc and poured into ice water, neutralized with a saturated aqueous Na_2CO_3 solution, and then extracted repeatedly into EtOAc. The organic fractions were pooled, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to yield 435 mg of a mixture of formamides **36a** and **36b**, which were carried onto the next step without further purification. This mixture of formamides **36a** and **36b** (435 mg) was charged with 1.0 N NaOH (30 mL), and then heated to 70 °C for 1 h, then 80 °C for an additional 3 h, and then cooled to room temperature for 12 h. An additional portion of 1.0 N NaOH (30 mL) was added, and the reaction was heated at 90 °C for 3 h. The reaction was then chilled in an ice water bath, then diluted with H_2O and extracted with EtOAc (3 × 250 mL). The organic fractions were pooled, washed with H_2O (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure, and then chromatographed on SiO_2 using a gradient that started with CH_2Cl_2 and ended with 90:9:1 CH_2Cl_2:MeOH:concentrated NH_4OH. Yield of **37**: 50 mg (11% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43–1.62 (m, 6H), 5.13 (bs, 2H), 6.52 (d, $J = 5.4$ Hz, 1H), 7.05–7.17 (m, 1H), 7.12 (t, $J = 8.6$ Hz, 2H), 7.60–7.68 (m, 2H), 7.77 (bs, 1H), 8.12 (d, $J = 5.4$ Hz, 1H), 9.43 (d, $J = 7.5$ Hz, 1H). MS (ESI+) 363.2.

*4.1.34. 2-[2-(4-Fluorophenyl)-3-(2-methylsulfanylpyrimidin-4-yl)imidazo[1,2-a]pyridin-7-yl]butyrontirile (**38**)*

A solution of nitrile **26** (2.00 g, 5.33 mmol) in THF (100 mL) was charged with NaH (234 mg of a 60% w/w suspension in mineral oil, 5.83 mmol), then bromoethane (871 mg, 597 μL, 8.00 mmol), and the reaction was stirred at room temperature for 12 h, and was then quenched with a saturated aqueous $NaHCO_3$ solution (200 mL) and extracted into EtOAc (3 × 200 mL). The organic fractions were pooled, dried over Na_2SO_4, filtered, concentrated under reduced pressure, and then chromatographed on SiO_2 using a gradient that started with CH_2Cl_2 and ended with 97:2.7:0.3 CH_2Cl_2:MeOH:concentrated NH_4OH. Yield of **38**: 660 mg (31%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (t, $J = 7.4$ Hz, 3H), 2.00–2.11 (m, 2H), 2.66 (s, 3H), 3.88 (t, $J = 7.0$ Hz, 1H), 6.84 (d, $J = 5.4$ Hz, 1H), 6.98 (dd, $J = 7.3$, 2.0 Hz, 1H), 7.16 (t, $J = 8.8$ Hz, 2H), 7.60–7.67 (m, 2H), 7.67–7.72 (m, 1H), 8.33 (d, $J = 5.4$ Hz, 1H), 9.63 (d, $J = 7.3$ Hz, 1H). MS (ESI+) 404.1.

*4.1.35. General procedure for the synthesis of sulfones **39a**, **39b**, and **39c***

A solution of appropriate sulfide in 1:1 MeOH:acetone was charged with a solution of OXONE® in H_2O, and allowed to stir at room temperature for 12 h. The reaction was then chilled to −40 °C in a CO_2/IPA bath. Excess sulfur dioxide gas was then bubbled in over 5 min. After stirring at −40 °C for an additional 15 min, the reaction was quenched with a saturated aqueous $NaHCO_3$ solution until basic to litmus paper, and then extracted repeatedly into EtOAc. The organic fractions were pooled, dried over Na_2SO_4, filtered, and concentrated under reduced pressure.

*4.1.35.1. [2-(4-Fluorophenyl)-3-(2-methanesulfonylpyrimidin-4-yl)imidazo[1,2-a]pyridin-7-yl]acetonitrile (**39a**).* Sulfone **39a** was prepared from sulfide **26** (1.00 g, 2.66 mmol) and OXONE® (10.0 g, 16.4 mmol dissolved in 150 mL H_2O) in 1:1 MeOH:acetone (300 mL). Yield of **39a**: 980 mg (91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.40 (s, 3H), 3.91 (s, 2H), 7.07 (d, $J = 7.6$ Hz, 1H), 7.20 (t, $J = 8.2$ Hz, 2H), 7.31 (d, $J = 5.6$ Hz, 1H), 7.57–7.65 (m, 2H), 7.77 (bs, 1H), 8.54 (d, $J = 5.6$ Hz, 1H), 9.92 (d, $J = 7.6$ Hz, 1H). MS (ESI+) 408.2.

*4.1.35.2. 2-[2-(4-Fluorophenyl)-3-(2-methanesulfonylpyrimidin-4-yl)imidazo[1,2-a]pyridin-7-yl]butyronitrile (**39b**).* Sulfone **39b** was prepared from sulfide **38** (660 mg, 1.64 mmol) and OXONE® (3.02 g, 4.92 mmol in 30 mL H_2O) in 1:1

MeOH:acetone (60 mL). Yield of **39b**: 630 mg (88%). MS (ESI+) 435.9.

*4.1.35.3. 2-[2-(4-Fluorophenyl)-3-(2-methanesulfonylpyrimidin-4-yl)imidazo[1,2-a]pyridin-7-yl]-2-methylpropiontirile (**39c**).* Sulfone **39c** was prepared from sulfide **27b** (2.20 g, 5.45 mmol) and OXONE® (10.0 g, 16.4 mmol in 150 mL H_2O) in 1:1 MeOH:acetone (200 mL). Yield of **39c**: 2.10 g (89%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.84 (s, 6H), 3.43 (s, 3H), 7.20–7.29 (m, 3H), 7.34 (d, $J = 5.5$ Hz, 1H), 7.61–7.69 (m, 2H), 7.90 (bs, 1H), 8.57 (d, $J = 5.5$ Hz, 1H), 9.97 (d, $J = 7.5$ Hz, 1H). MS (ESI+) 436.2.

*4.1.36. General procedure for the synthesis of primary amines **40a** and **40b***

A solution of appropriate nitrile in 9:1 EtOH:$CHCl_3$ in a pressure reactor was charged with platinum(IV) oxide, pressurized with hydrogen at 50 psi, and stirred at room temperature for 12 h. Additional platinum(IV) oxide was added as noted. The reaction was then filtered, concentrated under reduced pressure, and carried onto the next step without further purification.

*4.1.36.1. 2-[2-(4-Fluorophenyl)-3-(2-methanesulfonylpyrimidin-4-yl)imidazo[1,2-a]pyridin-7-yl]ethylamine (**40a**).* Primary amine **40a** was prepared from nitrile **39a** (980 mg, 2.41 mmol) and platinum(IV) oxide (200 mg, 0.881 mmol at $t = 0$ h, and 500 mg, 1.14 mmol at $t = 12$ h) in 9:1 EtOH:$CHCl_3$ (20 mL). Crude yield of **40a**: 1.20 g (>100%). MS (ESI+) 412.2.

*4.1.36.2. 2-[2-(4-Fluorophenyl)-3-(2-methanesulfonylpyrimidin-4-yl)imidazo[1,2-a]pyridin-7-yl]butylamine (**40b**).* Primary amine **40b** was prepared from nitrile **39b** (630 mg, 1.45 mmol) and platinum oxide (500 mg, 1.14 mmol) in 9:1 EtOH:$CHCl_3$ (50 mL). Crude yield of **40b**: 740 mg (>100%). MS (ESI+) 440.1.

*4.1.37. General procedure for the synthesis of 2-aminopyrimidines **40c**, **41a**, and **41b***

A suspension of appropriate sulfone in THF was chilled in a pressure reactor to −60 °C to −70 °C in a CO_2/IPA bath, and charged with excess ammonia gas. The pressure reactor was sealed, and the reaction was allowed to warm to room temperature with stirring for 12 h, during which the reaction pressure had reached 35–50 psi. The pressure was then released, and the reaction was concentrated under reduced pressure, and then chromatographed on SiO_2 using a gradient that started with CH_2Cl_2 and ended with 90:9:1 CH_2Cl_2:MeOH:concentrated NH_4OH.

*4.1.37.1. 3-[2-(2-Aminopyrimidin-4-yl)-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-7-yl]-2-methylpropiontirile (**40c**).* 2-Aminopyrimidine **40c** was prepared from sulfone **39c** (1.10 g, 2.53 mmol) and ammonia (49.0 g, 2.88 mol) in THF (100 mL). Yield of **40c**: 750 mg (80%). ^{1}H NMR 500 MHz, $CDCl_3$) δ 1.82 (s, 6H), 5.15 (bs, 2H), 6.56 (d, $J = 5.5$ Hz, 1H), 7.09 (dd, $J = 7.5$, 2.0 Hz, 1H), 7.15 (t, $J = 8.8$ Hz, 2H), 7.62–7.70 (m, 2H), 7.77 (bs, 1H), 8.17 (d, $J = 5.5$ Hz, 1H), 9.45 (d, $J = 7.5$ Hz, 1H). MS (ESI+) 373.4.

*4.1.37.2. 4-[7-(2-Aminoethyl)-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-ylamine (**41a**).* 2-Aminopyrimidine **41a** was prepared from sulfone **40a** (theoretically 1.20 g, 2.41 mmol) and ammonia (19.1 g, 1.12 mol) in THF (50 mL). Yield of **41a**: 214 mg (26% over two steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.87 (t, $J = 7.0$ Hz, 2H), 3.08 (t, $J = 7.0$ Hz, 2H), 5.14 (bs, 2H), 6.53 (d, $J = 5.2$ Hz, 1H), 6.82 (dd, $J = 7.0$, 1.5 Hz, 1H), 7.10–7.18 (m, 2H), 7.51 (bs, 1H), 7.61–7.69 (m, 2H), 8.13 (d, $J = 5.2$ Hz, 1H), 9.45 (d, $J = 7.0$ Hz, 1H). MS (ESI+) 349.3.

*4.1.37.3. 4-[7-(2-Aminomethylpropyl)-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-ylamine (**41b**).* 2-Aminopyrimidine **41b** was prepared from sulfone **40b** (theoretically 636 mg, 1.45 mmol) and ammonia (16.0, 1.17 mol) in THF (50 mL). Yield of **41b**: 40.0 mg (7.3% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, $J = 7.3$ Hz, 3H), 1.49–1.72 (m, 1H), 1.69–1.89 (m, 1H), 2.53–2.74 (m, 1H), 2.83–3.15 (m, 2H), 5.10 (bs, 2H), 6.53 (d, $J = 5.4$ Hz, 1H), 6.81 (d, $J = 7.1$Hz, 1H), 7.13 (t, $J = 8.4$ Hz, 2H), 7.51 (bs, 1H), 7.61–7.69 (m, 2H), 8.12 (d, $J = 5.4$ Hz, 1H), 9.46 (d, $J = 7.1$ Hz, 1H). MS (ESI+) 377.2.

*4.1.38. 4-[7-(2-Amino-1,1-dimethylethyl)-2-(4-fluorophenyl)-imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-ylamine (**41c**)*

A solution of nitrile **40c** (700 mg, 1.88 mmol) in THF (25 mL) was charged with $LiAlH_4$ (285 mg, 7.52 mmol). After stirring at room temperature for 45 min, the reaction was diluted with EtOAc (200 mL), treated with the slow addition of water (10 mL), and then charged with excess of 2:1 $Na_2SO_4 \cdot 10H_2O$:Celite. The mixture was filtered, then concentrated under reduced pressure, and then chromatographed on SiO_2 using a gradient that started with CH_2Cl_2 and ended with 90:9:1 CH_2Cl_2:MeOH:concentrated NH_4OH. Yield of **41c**: 196 mg (28%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.38 (s, 6H), 2.89 (s, 2H), 5.14 (bs, 2H), 6.54 (d, $J = 5.5$ Hz, 1H), 6.97 (dd, $J = 7.5$, 2.0 Hz, 1H), 7.10–7.18 (m, 2H), 7.61–7.69 (m, 3H), 8.13 (d, $J = 5.5$ Hz, 1H), 9.46 (d, $J = 7.5$ Hz, 1H). MS (ESI+) 377.2.

*4.1.39. General procedure for the synthesis of tertiary amines **42a**, **42b**, and **42c***

A solution of appropriate primary amine in CH_3OH was charged with formaldehyde, AcOH, and sodium cyanoborohydride. After stirring at room temperature for 3 h, the reaction was worked up (EtOAc, saturated $NaHCO_3$ solution), dried over Na_2SO_4, filtered, concentrated under reduced pressure, and then chromatographed on SiO_2 using a gradient that started with CH_2Cl_2 and ended with 90:9:1 CH_2Cl_2:MeOH:concentrated NH_4OH.

*4.1.39.1. 4-[7-(2-Dimethylaminoethyl)-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-ylamine (**42a**).* Dimethylamine **42a** was prepared from primary amine **41a** (100 mg, 0.287 mmol), formaldehyde (93 mg of a 37% w/w/

solution in H_2O, 0.34 mmol), AcOH (100 μL), and sodium cyanoborohydride (1.43 mL of a 1.0 M solution in THF, 1.43 mmol) in MeOH (3.0 mL). After chromatography on SiO_2, the product was purified further by HPLC using a MeOH/H_2O gradient, where the aqueous phase was 98:9.1:0.1 H_2O:CH_3CN:Et_3N. Yield of **42a**: 68.0 mg (63%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.33 (s, 6H), 2.64 (t, $J = 7.8$ Hz, 2H), 2.89 (t, $J = 7.8$ Hz, 2H), 5.11 (bs, 2H), 6.52 (d, $J = 5.5$ Hz, 1H), 6.83 (dd, $J = 7.0$, 2.0 Hz, 1H), 7.10–7.18 (m, 2H), 7.52 (bs, 1H), 7.61–7.69 (m, 2H), 8.12 (d, $J = 5.5$ Hz, 1H), 9.44 (dd, $J = 7.5$, 0.5 Hz, 1H). MS (ESI+) 377.4.

*4.1.39.2. 4-[7-(1-Dimethylaminomethylpropyl)-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-ylamine (**42b**).* Dimethylamine **42b** was prepared from primary amine **41b** (40.0 mg, 0.106 mmol), formaldehyde (34 mg of a 37% w/w solution in H_2O, 23 μL, 0.43 mmol), AcOH (35 mL), and sodium cyanoborohydride (531 μL of a 1.0 M in THF, 0.531 mmol) in MeOH (2.0 mL). Yield of **42b**: 20.0 mg (47%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.60–0.90 (m, 1H), 0.85 (t, $J = 7.4$ Hz, 3H), 1.47–1.68 (m, 1H), 1.70–1.93 (m, 1H), 2.25 (s, 6H), 2.62–2.75 (m, 1H), 2.73–2.90 (m, 1H), 5.09 (bs, 2H), 6.51 (d, $J = 5.4$ Hz, 1H), 6.81 (dd, $J = 7.3$, 1.8 Hz, 1H), 7.12 (t, $J = 8.7$ Hz, 2H), 7.48 (bs, 1H), 7.60–7.68 (m, 2H), 8.11 (d, $J = 5.4$ Hz, 1H), 9.46 (d, $J = 7.3$ Hz, 1H). MS (ESI+) 405.2.

*4.1.39.3. 4-[7-(2-Dimethylamino-1,1-dimethylethyl)-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-ylamine (**42c**).* Dimethylamine **42c** was prepared from primary amine **41c** (170 mg, 0.452 mmol), formaldehyde (110 mg of a 37% aqueous solution, 1.35 mmol), AcOH (170 μL), and sodium cyanoborohydride (2.26 mL of a 1.0 M solution in THF, 2.26 mmol) in MeOH (2.0 mL). After chromatography on SiO_2, the product was purified further by HPLC using a MeOH/H_2O gradient, where the aqueous phase was 98:9.1:0.1 H_2O:CH_3CN:Et_3N. Yield of **42c**: 104 mg (57%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.39 (s, 6H), 2.15 (s, 6H), 2.54 (s, 2H), 5.11 (bs, 2H), 6.54 (d, $J = 5.5$ Hz, 1H), 7.06 (dd, $J = 7.3$, 2.0 Hz, 1H), 7.09–7.17 (m, 2H), 7.62–7.71 (m, 3H), 8.12 (d, $J = 5.5$ Hz, 1H), 9.44 (d, $J = 7.3$ Hz, 1H). MS (ESI+) 405.3.

*4.1.40. 2-(4-Fluorophenyl)-7-(3-methyloxazolidin-5-yl)-3-(2-methylsulfanylpyrimidin-4-yl)imidazo-[1,2-a]pyridine (**43**)*

A solution of aldehyde **18** (1.44 g, 3.95 mmol) in toluene (120 mL) was charged with sarcosine (710 mg, 7.97 mmol) and paraformaldehyde (600 mg, 20.0 mmol), and the reaction was equipped with a Dean Stark trap and heated under reflux for 12 h. The reaction was then concentrated under reduced pressure, diluted with acetone, and then filtered through a 5 g SiO_2 cartridge, which was then washed with acetone (80 mL). The filtrate was then concentrated under reduced pressure, and not purified further. Yield of **43**: 1.65 g (98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.63 (bs, 6H), 2.90–2.98 (m, 1H), 3.51–3.59 (m, 1H), 4.61–4.68 (m, 1H), 4.67–4.72 (m, 1H), 5.13–5.22 (m, 1H), 6.80 (d, $J = 5.4$ Hz, 1H), 6.97 (d, $J = 7.6$ Hz, 1H), 7.13 (t, $J = 8.4$ Hz, 2H), 7.57–7.64 (m, 2H), 7.69 (bs, 1H), 8.29 (d, $J = 5.4$ Hz, 1H), 9.56 (d, $J = 7.6$ Hz, 1H). MS (ESI+) 410.2 (under MS conditions, the aminal bond is cleaved and instead an M + 1 peak is observed for the resulting 7-C(OH)HCH$_2$N(Me)H product).

*4.1.41. 2-Dimethylamino-1-[2-(4-fluorophenyl)-3-(2-methylsulfanylpyrimidin-4-yl)imidazo[1,2-a]pyridin-7-yl]-ethanol (**44**)*

A solution of oxazolidine **43** (1.65 g, 3.91 mmol) in EtOH (50 mL) was charged with $NaBH_4$ (450 mg, 11.9 mmol), and stirred at room temperature for 3 h. The reaction was then quenched with a 20% w/v aqueous NH_4Cl solution (16 mL) and concentrated under reduced pressure, then diluted with H_2O and neutralized with an aqueous K_2CO_3 solution, and then extracted with CH_2Cl_2 (3 × 50 mL). The organic extracts were then pooled, dried over $MgSO_4$, filtered, and concentrated under reduced pressure, and then chromatographed on SiO_2 using a gradient that started with CH_2Cl_2 and ended with 90:9:1 CH_2Cl_2:MeOH:concentrated NH_4OH. Yield of **44**: 1.01 g (60%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.21 (s, 6H), 2.49 (m, 2H), 2.58 (s, 3H), 4.74–4.81 (m, 1H), 5.40 (bs, 1H), 6.86 (d, $J = 5.6$ Hz, 1H), 7.16 (dd, $J = 7.2$, 1.6 Hz, 1H), 7.29 (t, $J = 8.8$ Hz, 2H), 7.60–7.68 (m, 3H), 8.45 (d, $J = 5.6$ Hz, 1H), 9.32 (d, $J = 7.2$ Hz, 1H). MS (ESI+) 424.2.

*4.1.42. {2-Fluoro-2-[2-(4-fluorophenyl)-3-(2-methylsulfanylpyrimidin-4-yl)imidazo[1,2-a]pyridin-7-yl]ethyl}-dimethylamine (**45**)*

A solution of alcohol **44** (134 mg, 0.316 mmol) in CH_2Cl_2 (5.0 mL) was cooled to −78 °C in a CO_2/IPA bath, and then charged with diethylaminosulfur trifluoride (51 mg, 42 μL, 0.32 mmol), then allowed to warm to room temperature and stir for 2 h. The reaction was then washed with H_2O, dried over $MgSO_4$, filtered, and concentrated under reduced pressure, and then chromatographed on SiO_2 using a gradient that started with CH_2Cl_2 and ended with 90:9:1 CH_2Cl_2:MeOH:concentrated NH_4OH. Yield of **45**: 44 mg (32%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46 (s, 6H), 2.64 (s, 3H), 2.74–3.01 (m, 2H), 5.70–5.88 (m, 1H), 6.82 (d, $J = 5.4$ Hz, 1H), 7.00 (dd, $J = 7.3$, 1.5 Hz, 1H), 7.14 (t, $J = 8.6$ Hz, 2H), 7.58–7.66 (m, 2H), 7.69 (bs, 1H), 8.30 (d, $J = 5.4$ Hz, 1H), 9.59 (d, $J = 7.3$ Hz, 1H).

*4.1.43. {2-Fluoro-2-[2-(4-fluorophenyl)-3-(2-methanesulfonylpyrimidin-4-yl)imidazo[1,2-a]pyridin-7-yl]ethyl}-dimethylamine (**46**)*

A solution of sulfide **45** (59 mg, 0.14 mmol) in 1:1 MeOH:acetone (4.0 mL) was charged with a solution of OXONE® (256 mg, 0.417 mmol) in water (2.0 mL), and the reaction was allowed to stir for 12 h at room temperature. The reaction was then cooled to −78 °C in a CO_2/IPA bath, and charged with excess sulfur dioxide for 5 min. After stirring at room temperature for an additional 2 h, the reaction was concentrated under reduced pressure, diluted with H_2O, and treated with

a saturated aqueous $NaHCO_3$ solution until pH = 8. The mixture was then extracted with 9:1 CH_2Cl_2:MeOH (3 × 20 mL). The organic fractions were pooled, dried over Na_2SO_4, filtered, and concentrated under reduced pressure, and not purified further. Crude yield of **46**: 102 mg (>100%). MS (ESI+) 457.9.

4.1.44. 4-[7-(2-Dimethylamino-1-fluoroethyl)-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-ylamine (*47*)

A suspension of crude sulfone **46** (theoretically 64 mg, 0.14 mmol) in THF (20 mL) in a pressure reactor was chilled to −78 °C in a CO_2/IPA bath, and excess ammonia was bubbled in over 5 min. The pressure reactor was sealed, and the reaction was allowed to warm to room temperature with stirring for 12 h. The pressure was then released, and the reaction was concentrated under reduced pressure, and then chromatographed on SiO_2 using a gradient that started with CH_2Cl_2 and ended with 90:9:1 CH_2Cl_2:MeOH:concentrated NH_4OH. Yield of **47**: 95 mg (44% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.40 (s, 6H), 2.62–2.77 (m, 1H), 2.82–2.98 (m, 1H), 5.15 (bs, 2H), 5.58–5.78 (m, 1H), 6.53 (d, J = 5.3 Hz, 1H), 6.93 (dd, J = 7.3, 1.7 Hz, 1H), 7.13 (t, J = 8.7 Hz, 2H), 7.61–7.70 (m, 3H), 8.15 (d, J = 5.3 Hz, 1H), 9.49 (d, J = 7.3 Hz, 1H). MS (ESI+) 395.2.

4.1.45. 2-Chloro-1-(4-fluorophenyl)ethanone O-methyloxime (*49*) and 2-bromo-1-(4-fluorophenyl)ethanone O-methyloxime (*49*)

A solution of 4-fluorophenacyl chloride (100 g, 579 mmol) in MeOH (1.0 L) was charged with *O*-methylhydroxylamine hydrochloride (96.8 g, 1.56 mol), and was then heated to 65 °C for 2 h. The reaction with crude **48** was then concentrated under reduced pressure, then charged with acetone (750 mL) and LiBr (252 g, 2.90 mol), and heated to 60 °C for 16 h. The reaction was then concentrated under reduced pressure, suspended in CH_2Cl_2 (1.0 L), and washed with H_2O (3 × 200 mL). The organic extracts were then pooled, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Yield of **49**: 118 g (83% over two steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.10 (s, 3H), 4.35 (s, 2H), 7.11 (t, J = 8.8 Hz, 2H), 7.69–7.75 (m, 2H). MS (ESI+) 246.0.

4.1.46. 3-[2-(4-Fluorophenyl)imidazo[1,2-a]pyridin-7-yl]propan-1-ol (*50*)

A solution of 3-(pyridin-4-yl)propan-1-ol (7.00 g, 51.0 mmol) in acetone (250 mL) was charged with bromide **49** (12.5 g, 51.0 mmol), and the reaction was stirred at room temperature for 12 h. The intermediate salt was filtered, then dissolved in THF (150 mL) and charged with DBU (5.96 g, 5.85 mL, 39.1 mmol), and the reaction was heated to reflux for 3 h. The reaction was then concentrated under reduced pressure, diluted in CH_2Cl_2, and washed with H_2O. The organic layer was dried with Na_2SO_4, filtered, and concentrated under reduced pressure, and then chromatographed on SiO_2 using a gradient that started with CH_2Cl_2 and ended with 90:9:1 CH_2Cl_2:MeOH:concentrated NH_4OH. Yield of **50**: 2.00 g (23%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.76–1.86 (m, 2H), 2.64 (t, J = 7.8 Hz, 2H), 3.59 (t, J = 6.3 Hz, 2H), 6.52 (d, J = 6.9 Hz, 1H), 7.00 (t, J = 8.7 Hz, 2H), 7.27 (bs, 1H), 7.59 (bs, 1H), 7.77 (m, 2H), 7.86 (d, J = 6.9 Hz, 1H). MS (ESI+) 270.9.

4.1.47. Methanesulfonic acid 3-[2-(4-fluorophenyl)imidazo-[1,2-a]pyridin-7-yl]propyl ester (*51*)

A solution of alcohol **50** (600 mg, 2.22 mmol) in CH_2Cl_2 (20 mL) was chilled to 0 °C in an ice water bath, then charged with Et_3N (269 mg, 371 mL, 2.66 mmol) and methanesulfonyl chloride (279 mg, 189 mL), then allowed to warm to room temperature and stir for 2 h. The reaction was diluted with 9:1 CH_2Cl_2:MeOH and washed with H_2O, then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Crude methanesulfonate ester **51** was carried onto the next step without further purification.

4.1.48. {3-[2-(4-Fluorophenyl)imidazo[1,2-a]pyridin-7-yl]propyl}dimethylamine (*52*)

A solution of crude methanesulfonate ester **51** (theoretically 773 mg, 2.22 mmol) in CH_2Cl_2 (10 mL) was charged with diisopropylethylamine (513 mg, 773 μL, 4.44 mmol) and dimethylamine (773 μL of a 2.0 M in THF, 4.44 mmol). After stirring at room temperature for 2 h, a second portion of dimethylamine (773 μL of a 2.0 M in THF, 4.44 mmol) was added, and the reaction was stirred at room temperature for an additional 12 h. The reaction was then concentrated under reduced pressure, and then chromatographed on SiO_2 using a gradient that started with CH_2Cl_2 and ended with 90:9:1 CH_2Cl_2:MeOH:concentrated NH_4OH. Yield of **52**: 720 mg (78% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.67–1.77 (m, 2H), 2.11 (s, 6H), 2.21 (t, J = 7.2 Hz, 2H), 2.56 (t, J = 7.6 Hz, 2H), 6.54 (dd, J = 6.9, 1.4 Hz, 1H), 6.99 (t, J = 8.7 Hz, 2H), 7.27 (bs, 1H), 7.60 (bs, 1H), 7.72–7.81 (m, 2H), 7.89 (d, J = 6.9 Hz, 1H). MS (ESI+) 297.9.

4.1.49. 1-[7-(3-Dimethylaminopropyl)-2-(4-fluorophenyl)-imidazo[1,2-a]pyridin-3-yl]ethanone (*53*)

A solution of imidazopyridine **52** (170 mg, 0.572 mmol) in acetic anhydride (10.0 mL) was charged with concentrated H_2SO_4 (four drops) and heated to 160 °C for 12 h. The reaction was then concentrated under reduced pressure, and then chromatographed on SiO_2 using a gradient that started with CH_2Cl_2 and ended with 90:9:1 CH_2Cl_2:MeOH:concentrated NH_4OH. Yield of **53**: 80.0 mg (41%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.80–1.93 (m, 2H), 2.17 (s, 3H), 2.23 (s, 6H), 2.27–2.37 (m, 2H), 2.79 (t, J = 7.6 Hz, 2H), 6.96 (dd, J = 7.1, 1.6 Hz, 1H), 7.19 (t, J = 8.7 Hz, 2H), 7.51 (bs, 1H), 7.57 (m, 2H), 9.65 (d, J = 7.1 Hz, 1H). MS (ESI+) 340.1.

4.1.50. 3-Dimethylamino-1-[7-(3-dimethylaminopropyl)-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]propenone (*54*)

A solution of ketone **53** (290 mg, 0.850 mmol) in DMFDMA (509 mg, 567 μL, 4.27 mmol) was heated to

110 °C for 12 h. The reaction was then concentrated under reduced pressure, and then chromatographed on SiO_2 using a gradient that started with CH_2Cl_2 and ended with 90:9:1 CH_2Cl_2:MeOH:concentrated NH_4OH, and carried directly onto the next step. Yield of **54**: 100 mg (30%). MS (ESI+) 395.2.

*4.1.51. 4-[7-(3-Dimethylaminopropyl)-2-(4-fluorophenyl)-imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-ylamine (**55**)*

A solution of enone **54** (97 mg, 0.24 mmol) in DMF (6.0 mL) was charged with guanidine hydrochloride (27 mg, 0.28 mmol) and K_2CO_3 (39 mg, 0.28 mmol), and the reaction was heated to 110 °C for 12 h. The reaction was then diluted with 9:1 CH_2Cl_2:MeOH, and washed with a saturated aqueous $NaHCO_3$ solution, then saturated aqueous LiCl solution, then dried over Na_2SO_4, filtered, and concentrated under reduced pressure, and then chromatographed on SiO_2 using a gradient that started with CH_2Cl_2 and ended with 90:9:1 CH_2Cl_2:MeOH: concentrated NH_4OH. Yield of **55**: 27 mg (28%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.83–1.93 (m, 2H), 2.27 (s, 6H), 2.32–2.39 (m, 2H), 2.77 (t, $J = 7.6$ Hz, 2H), 5.09 (bs, 2H), 6.52 (d, $J = 5.5$ Hz, 1H), 6.81 (dd, $J = 7.3$, 1.8 Hz, 1H), 7.13 (t, $J = 8.9$ Hz, 2H), 7.48 (bs, 1H), 7.60–7.67 (m, 2H), 8.12 (d, $J = 5.5$ Hz, 1H), 9.43 (d, $J = 7.3$ Hz, 1H). MS (ESI+) 391.3.

*4.1.52. 1-(3,4,5,6-Tetrahydro-2H-[4,4′]bipyridin-1-yl)-ethanone (**56**)*

A solution of 1,2,3,4,5,6-hexahydro-[4,4′]bipyridinyl (3.01 g, 18.6 mmol) in acetic anhydride was stirred at room temperature for 12 h, and was then concentrated under reduced pressure, diluted with CH_2Cl_2 (250 mL), washed with a saturated aqueous $NaHCO_3$ solution (3 × 50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Yield of **56**: 2.99 g (79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54–1.72 (m, 2H), 1.92 (t, $J = 13.6$ Hz, 2H), 2.14 (s, 3H), 2.58–2.70 (m, 1H), 2.70–2.83 (m, 1H), 3.14–3.25 (m, 1H), 3.91–4.02 (m, 1H), 4.75–4.88 (m, 1H), 7.15 (d, $J = 5.9$ Hz, 2H), 8.55 (d, $J = 5.9$ Hz, 2H). MS (ESI+) 204.9.

*4.1.53. 1-{4-[2-(4-Fluorophenyl)imidazo[1,2-a]pyridin-7-yl]piperidin-1-yl}ethanone (**57**)*

A solution of pyridine **56** (2.97 g, 14.5 mmol) in acetone (100 mL) was charged with α-bromo-*O*-methyloxime **49** (3.57 g, 14.5 mmol), and the reaction was stirred at room temperature for 12 h, then concentrated under reduced pressure, diluted with MeOH (100 mL), charged with *t*-BuOK (1.95 g, 17.4 mmol), and heated to 80 °C for 12 h. The reaction was then concentrated under reduced pressure, and chromatographed on SiO_2 using a gradient that started with CH_2Cl_2 and ended with 90:9:1 CH_2Cl_2:MeOH:concentrated NH_4OH. Yield of **57**: 3.05 g (62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.57–1.73 (m, 2H), 1.92–2.04 (m, 2H), 2.16 (s, 3H), 2.62–2.72 (m, 1H), 2.76–2.86 (m, 1H), 3.17–3.27 (m, 1H), 3.94–4.04 (m, 1H), 4.79–4.88 (m, 1H), 6.69 (dd, $J = 7.1$, 1.0 Hz, 1H), 7.13 (t, $J = 8.7$ Hz, 2H), 7.46 (s, 1H), 7.77 (s, 1H), 7.89–7.96 (m, 2H), 8.08 (d, $J = 7.1$ Hz, 1H). MS (ESI+) 338.1.

*4.1.54. 1-{4-[3-Acetyl-2-(4-fluorophenyl)imidazo[1,2-a]-pyridin-7-yl]piperidin-1-yl}ethanone (**58**)*

A solution of imidazopyridine **57** (3.04 g, 9.01 mmol) in acetic anhydride (100 mL) was charged with concentrated H_2SO_4 (three drops) and heated to 160 °C for 12 h. The reaction was then concentrated under reduced pressure, and then chromatographed on SiO_2 using a gradient that started with CH_2Cl_2 and ended with 90:9:1 CH_2Cl_2:MeOH:concentrated NH_4OH. Yield of **58**: 1.43 g (43%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.61–1.77 (m, 2H), 1.96–2.06 (m, 2H), 2.17 (s, 3H), 2.20 (s, 3H), 2.64–2.73 (m, 1H), 2.86–2.95 (m, 1H), 3.18–3.28 (m, 1H), 4.01 (d, $J = 13.4$ Hz, 1H), 4.86 (dd, $J = 13.4$, 1.6 Hz, 1H), 6.98 (dd, $J = 7.2$, 1.4 Hz, 1H), 7.21 (t, $J = 8.6$ Hz, 2H), 7.55–7.62 (m, 2H), 7.56 (s, 1H), 9.70 (d, $J = 7.2$ Hz, 1H). MS (ESI+) 379.9.

*4.1.55. 1-[7-(1-Acetylpiperidin-4-yl)-2-(4-fluorophenyl)-imidazo[1,2-a]pyridin-3-yl]-3-dimethylamino-propenone (**59**)*

A solution of ketone **58** (1.43 g, 3.77 mmol) in DMFDMA (50 mL) was heated to 110 °C for 12 h, then concentrated under reduced pressure, and then chromatographed on SiO_2 using a gradient that started with CH_2Cl_2 and ended with 90:9:1 CH_2Cl_2:MeOH:concentrated NH_4OH. Yield of **59**: 1.41 g (86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58–1.78 (m, 2H), 1.99 (t, $J = 12.3$ Hz, 2H), 2.16 (s, 3H), 2.48 (bs, 3H), 2.62–2.74 (m, 1H), 2.79–2.90 (m, 1H), 3.05 (bs, 3H), 3.16–3.27 (m, 1H), 3.99 (bd, $J = 13.4$ Hz, 1H), 4.83 (bd, $J = 13.4$ Hz, 1H), 5.11 (d, $J = 12.5$ Hz, 1H), 6.83 (dd, $J = 7.3$, 1.6 Hz, 1H), 7.14 (t, $J = 8.7$ Hz, 2H), 7.45 (bs, 1H), 7.63 (d, $J = 12.5$ Hz, 1H), 7.66–7.74 (m, 2H), 9.58 (d, $J = 7.3$ Hz, 1H). MS (ESI+) 435.1.

*4.1.56. 1-{4-[3-(2-Aminopyrimidin-4-yl)-2-(4-fluorophenyl)-imidazo[1,2-a]pyridin-7-yl]piperidin-1-yl}ethanone (**60**)*

A solution of enone **59** (1.41 g, 3.24 mmol) in 1-propanol (100 mL) was charged with guanidine hydrochloride (465 mg, 4.87 mmol) and sodium methoxide (1.05 g of a 25% w/w solution in MeOH, 1.11 mL, 4.87 mmol), and the reaction was heated to 100 °C for 12 h. The reaction was then concentrated under reduced pressure, suspended in H_2O (50 mL), and extracted into 4:1 CH_2Cl_2:MeOH (3 × 250 mL). The organic fractions were pooled, dried over Na_2SO_4, filtered, concentrated under reduced pressure, and then chromatographed on SiO_2 using a gradient that started with CH_2Cl_2 and ended with 90:9:1 CH_2Cl_2:MeOH:concentrated NH_4OH. Yield of **60**: 1.01 g (72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.57–1.74 (m, 2H), 1.98 (t, $J = 12.7$ Hz, 2H), 2.15 (s, 3H), 2.63–2.73 (m, 1H), 2.79–2.89 (m, 1H), 3.17–3.28 (m, 1H), 3.98 (d, $J = 13.5$ Hz, 1H), 4.83 (d, $J = 13.5$ Hz, 1H), 5.22 (bs, 2H), 6.51 (d, $J = 5.4$ Hz, 1H), 6.78 (dd, $J = 7.3$, 1.6 Hz, 1H), 7.12 (t, $J = 8.7$ Hz, 2H), 7.47 (bs, 1H), 7.59–7.67 (m, 2H), 8.11 (d, $J = 5.4$ Hz, 1H), 9.43 (d, $J = 7.3$ Hz, 1H). MS (ESI+) 430.8.

*4.1.57. 4-[2-(4-Fluorophenyl)-7-piperidin-4-ylimidazo-[1,2-a]pyridin-3-yl]piperidin-2-ylamine (**61**)*

Amide **60** (990 mg, 2.30 mmol) was charged with 3 N HCl (40 mL) and heated to 90 °C for 12 h. The reaction was then concentrated under reduced pressure, diluted to 10 mL in MeOH, treated with concentrated NH_4OH until basic to litmus paper, and then purified by HPLC using a MeOH/H_2O gradient, where the aqueous phase was 98.9:1.0:0.1 H_2O:CH_3CN:Et_3N. Yield of **61**: 467 mg (52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.66–1.81 (m, 2H), 1.94 (bd, $J = 12.8$ Hz, 2H), 2.69–2.80 (m, 1H), 2.77–2.87 (m, 2H), 3.28 (bd, $J = 12.1$ Hz, 2H), 5.12 (bs, 2H), 6.51 (d, $J = 5.4$ Hz, 1H), 6.85 (dd, $J = 7.3$, 1.6 Hz, 1H), 7.12 (t, $J = 8.7$ Hz, 2H), 7.50 (bs, 1H), 7.58–7.70 (m, 2H), 8.11 (d, $J = 5.4$ Hz, 1H), 9.44 (d, $J = 7.3$ Hz, 1H). MS (ESI+) 388.8.

*4.1.58. General procedure for the synthesis of N-substituted piperidines **62a** and **62d–k** (Method A)*

A solution of secondary amine **61** in MeOH (8.0 mL) was charged with AcOH, appropriate aldehyde, and sodium cyanoborohydride (1.0 M solution in THF). After stirring at room temperature for 6 h, additional aldehyde was added if the reaction was not yet complete, and all reactions then stirred for an additional 12 h at room temperature. Each reaction was then treated with excess concentrated NH_4OH (500 μL), then purified by HPLC using a MeOH/H_2O gradient, where the aqueous phase was 98.9:1.0:0.1 H_2O:CH_3CN:Et_3N. Any modifications to this procedure are noted below.

*4.1.59. General procedure for the synthesis of N-substituted piperidines **62b** and **62c** (Method B)*

A solution of secondary amine **61** in EtOH (10 mL) was charged with K_2CO_3 and appropriate alkyl bromide, and heated to 90 °C for 24 h. If necessary, additional alkyl halide was then added, and heating continued for another 24 h. The reaction was then purified by HPLC using a MeOH/H_2O gradient, where the aqueous phase was 98.9:1.0:0.1 H_2O:CH_3CN:Et_3N. Any modifications to this procedure are noted below.

*4.1.59.1. 4-[7-(1-Ethylpiperidin-4-yl)-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-ylamine (**62a**).* Compound **62a** was prepared by Method A from amine **61** (40.0 mg, 0.103 mmol), AcOH (40 μL), acetaldehyde (5.0 mg, 7.0 μL, 0.12 mmol at $t = 0$ h, then an additional 3 μL at $t = 6$ h), and sodium cyanoborohydride (113 μL of a 1.0 M solution in THF, 0.113 mmol). Yield of **62a**: 27.5 mg (53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 (t, $J = 7.2$ Hz, 3H), 1.71–2.13 (m, 6H), 2.48 (q, $J = 7.2$ Hz, 2H), 2.55–2.66 (m, 1H), 3.05–3.20 (m, 2H), 5.14 (bs, 2H), 6.51 (d, $J = 5.4$ Hz, 1H), 6.84 (dd, $J = 7.2$, 1.9 Hz, 1H), 7.12 (t, $J = 8.7$ Hz, 2H), 7.50 (bs, 1H), 7.60–7.68 (m, 2H), 8.11 (d, $J = 5.4$ Hz, 1H), 9.42 (d, $J = 7.2$ Hz, 1H). MS (ESI+) 417.2.

*4.1.59.2. 2-{4-[3-(2-Aminopyrimidin-4-yl)-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-7-yl]piperidin-1-yl}ethanol (**62b**).* Compound **62b** was prepared by Method B from amine **61** (40.0 mg, 0.103 mmol), K_2CO_3 (21.0 mg, 0.154 mmol), and 2-bromoethanol (15 mg, 9.0 μL, 0.12 mmol). Yield of **62b**: 23.4 mg (53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.80–2.00 (m, 5H), 2.28 (t, $J = 11.3$ Hz, 2H), 2.64 (t, $J = 5.2$ Hz, 2H), 3.12 (d, $J = 11.3$ Hz, 2H), 3.69 (t, $J = 5.2$ Hz, 2H), 5.11 (bs, 2H), 6.52 (d, $J = 5.4$ Hz, 1H), 6.85 (d, $J = 7.2$ Hz, 1H), 7.13 (t, $J = 8.5$ Hz, 2H), 7.50 (bs, 1H), 7.60–7.68 (m, 2H), 8.12 (d, $J = 5.4$ Hz, 1H), 9.44 (d, $J = 7.2$ Hz, 1H). MS (ESI+) 433.1.

*4.1.59.3. 2-{4-[3-(2-Aminopyrimidin-4-yl)-2-(4-fluorophenyl)-imidazo[1,2-a]pyridin-7-yl]piperidin-1-yl}propan-1-ol (**62c**).* Compound **62c** was prepared by Method B from amine **61** (40.0 mg, 0.103 mmol), K_2CO_3 (21.0 mg, 0.154 mmol), and 3-bromopropan-1-ol (15 mg, 9.0 μL, 0.12 mmol at $t = 0$ h, then an additional 11 μL at $t = 24$ h, and 22 μL at $t = 48$ h, while heating at 90 °C for a total of 72 h). Yield of **63c**: 32.2 mg (70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.61–1.86 (m, 4H), 1.75–2.00 (m, 2H), 2.11 (t, $J = 11.3$ Hz, 2H), 2.55–2.70 (m, 1H), 2.67 (t, $J = 5.6$ Hz, 2H), 3.23 (d, $J = 11.3$ Hz, 2H), 3.84 (t, $J = 5.1$Hz, 2H), 5.14 (bs, 2H), 6.51 (d, $J = 5.3$ Hz, 1H), 6.81 (d, $J = 7.3$ Hz, 1H), 7.12 (t, $J = 8.5$ Hz, 2H), 7.48 (bs, 1H), 7.59–7.66 (m, 2H), 8.11 (d, $J = 5.3$ Hz, 1H), 9.42 (d, $J = 7.3$ Hz, 1H). MS (ESI+) 447.2.

*4.1.59.4. 4-[2-(4-Fluorophenyl)-7-(1-isobutylpiperidin-4-yl)-imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-ylamine (**62d**).* Compound **62d** was prepared by Method A from amine **61** (40.0 mg, 0.103 mmol), AcOH (40 μL), 2-methylpropionaldehyde (9.0 mg, 11 μL, 0.12 mmol at $t = 0$ h, then an additional 2.0 μL at $t = 6$ h), and sodium cyanoborohydride (113 μL of a 1.0 M solution in THF, 0.113 mmol). Yield of **62d**: 38.1 mg (69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (d, $J = 6.5$ Hz, 6H), 1.73–1.97 (m, 5H), 1.97–2.25 (m, 4H), 2.50–2.76 (m, 1H), 2.90–3.30 (m, 2H), 5.10 (bs, 2H), 6.51 (d, $J = 5.4$ Hz, 1H), 6.87 (d, $J = 7.1$ Hz, 1H), 7.12 (t, $J = 8.7$ Hz, 2H), 7.50 (bs, 1H), 7.60–7.68 (m, 2H), 8.11 (d, $J = 5.4$ Hz, 1H), 9.42 (d, $J = 7.1$ Hz, 1H). MS (ESI+) 445.3.

*4.1.59.5. 4-[7-(1-Cyclopropylmethylpiperidin-4-yl)-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-ylamine (**62e**).* Compound **62e** was prepared by Method A from amine **61** (40.0 mg, 0.103 mmol), AcOH (40 μL), cyclopropanecarbaldehyde (9.0 mg, 9.0 μL, 0.12 mmol), and sodium cyanoborohydride (113 μL of a 1.0 M solution in THF, 0.113 mmol). Yield of **62e**: 34.3 mg (62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.16 (q, $J = 5.0$ Hz, 2H), 0.57 (dd, $J = 12.8$, 5.0 Hz, 2H), 0.81–1.09 (m, 1H), 1.80–2.00 (m, 4H), 2.14 (t, $J = 10.4$ Hz, 2H), 2.35 (d, $J = 6.4$ Hz, 2H), 2.50–2.74 (m, 1H), 3.27 (d, $J = 11.1$ Hz, 2H), 5.12 (bs, 2H), 6.51 (d, $J = 5.4$ Hz, 1H), 6.87 (dd, $J = 7.3$, 1.5 Hz, 1H), 7.12 (t, $J = 8.7$ Hz, 2H), 7.51 (bs, 1H), 7.60–7.68 (m, 2H), 8.11 (d, $J = 5.4$ Hz, 1H), 9.43 (d, $J = 7.3$ Hz, 1H). MS (ESI+) 443.3.

*4.1.59.6. 4-{2-(4-Fluorophenyl)-7-[1-(2-methylbutyl)piperidin-4-yl]imidazo[1,2-a]pyridin-3-yl}pyrimidin-2-ylamine (**62f**).* Compound **62f** was prepared by Method A from amine **61** (40.0 mg, 0.103 mmol), AcOH (40 μL), 2-methylbutyraldehyde

(11 mg, 13 μL, 0.12 mmol at $t = 0$ h, then an additional 2.0 μL at $t = 6$ h), and sodium cyanoborohydride (113 μL of a 1.0 M solution in THF, 0.113 mmol). Yield of **62f**: 36.5 mg (64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.75–1.00 (m, 6H), 1.10–1.40 (m, 1H), 1.34–1.51 (m, 1H), 1.70–2.30 (m, 9H), 2.59 (t, $J = 9.8$ Hz, 1H), 2.91–3.15 (m, 2H), 5.09 (bs, 2H), 6.51 (d, $J = 5.4$ Hz, 1H), 6.86 (d, $J = 7.1$ Hz, 1H), 7.12 (t, $J = 8.7$ Hz, 2H), 7.50 (bs, 1H), 7.60–7.68 (m, 2H), 8.11 (d, $J = 5.4$ Hz, 1H), 9.42 (d, $J = 7.1$ Hz, 1H). MS (ESI+) 459.3.

*4.1.59.7. 4-[7-[1-(3,3-Dimethylbutyl)piperidin-4-yl)-2-(4-fluorophenyl)imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-ylamine (**62g**).* Compound **62g** was prepared by Method A from amine **61** (40.0 mg, 0.103 mmol), AcOH (40 μL), 3,3-dimethylbutyraldehyde (12 mg, 16 μL, 0.12 mmol), and sodium cyanoborohydride (113 μL of a 1.0 M solution in THF, 0.113 mmol). Yield of **62g**: 34.5 mg (58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (s, 9H), 1.40–1.55 (m, 2H), 1.73–1.98 (m, 4H), 2.00–2.19 (m, 2H), 2.28–2.47 (m, 2H), 2.52–2.70 (m, 1H), 3.13 (d, $J = 11.2$ Hz, 2H), 5.10 (bs, 2H), 6.51 (d, $J = 5.4$ Hz, 1H), 6.86 (dd, $J = 7.2$, 1.3 Hz, 1H), 7.12 (t, $J = 8.6$ Hz, 2H), 7.51 (bs, 1H), 7.64 (m, 2H), 8.11 (d, $J = 5.4$ Hz, 1H), 9.43 (d, $J = 7.2$ Hz, 1H). MS (ESI+) 473.3.

*4.1.59.8. 4-{2-(4-Fluorophenyl)-7-[1-(2-methylpentyl)piperidin-4-yl]imidazo[1,2-a]pyridin-3-yl}pyrimidin-2-ylamine (**62h**).* Compound **62h** was prepared by Method A from amine **61** (40.0 mg, 0.103 mmol), AcOH (40 μL), 2-methylpentanal (12 mg, 15 μL, 0.12 mmol at $t = 0$ h, then an additional 4.0 μL at $t = 6$ h), and sodium cyanoborohydride (113 μL of a 1.0 M solution in THF, 0.113 mmol). Yield of **62h**: 38.8 mg (66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85–0.97 (m, 6H), 1.03–1.15 (m, 1H), 1.22–1.49 (m, 3H), 1.61–1.75 (m, 1H), 1.75–1.95 (m, 4H), 1.93–2.28 (m, 4H), 2.49–2.67 (m, 1H), 3.02 (t, $J = 11.5$ Hz, 2H), 5.11 (bs, 2H), 6.51 (d, $J = 5.4$ Hz, 1H), 6.86 (dd, $J = 7.3$, 1.6 Hz, 1H), 7.12 (t, $J = 8.7$ Hz, 2H), 7.50 (bs, 1H), 7.60–7.68 (m, 2H), 8.11 (d, $J = 5.4$ Hz, 1H), 9.42 (d, $J = 7.3$ Hz, 1H). MS (ESI+) 473.4.

*4.1.59.9. 4-[2-(4-Fluorophenyl)-7-(1-hexylpiperidin-4-yl)-imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-ylamine (**62i**).* Compound **62i** was prepared by Method A from amine **61** (40.0 mg, 0.103 mmol), AcOH (40 μL), hexanal (12 mg, 15 μL, 0.12 mmol at $t = 0$ h, then an additional 4.0 μL at $t = 6$ h), and sodium cyanoborohydride (113 μL of a 1.0 M solution in THF, 0.113 mmol). Yield of **62i**: 38.6 mg (65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, $J = 6.6$ Hz, 3H), 1.32 (bs, 6H), 1.50–1.63 (m, 2H), 1.75–1.98 (m, 4H), 1.98–2.14 (m, 2H), 2.33–2.45 (m, 2H), 2.54–2.71 (m, 1H), 3.12 (d, $J = 10.1$ Hz, 2H), 5.10 (bs, 2H), 6.51 (d, $J = 5.4$ Hz, 1H), 6.86 (dd, $J = 7.3$, 1.3 Hz, 1H), 7.12 (t, $J = 8.7$ Hz, 2H), 7.51 (bs, 1H), 7.64 (dd, $J = 8.7$, 5.5 Hz, 2H), 8.11 (d, $J = 5.4$ Hz, 1H), 9.43 (d, $J = 7.3$ Hz, 1H). MS (ESI+) 473.4.

*4.1.59.10. 4-[7-(1-Benzylpiperidin-4-yl)-2-(4-fluorophenyl)-imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-ylamine (**62j**).* Compound **62j** was prepared by Method A from amine **61** (40.0 mg, 0.103 mmol), AcOH (40 μL), benzaldehyde (13 mg, 13 μL, 0.12 mmol at $t = 0$ h, then an additional 7.0 μL at $t = 6$ h), and sodium cyanoborohydride (113 μL of a 1.0 M solution in THF, 0.113 mmol). Yield of **62j**: 35.4 mg (60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.88 (q, $J = 12.0$ Hz, 4H), 2.15 (t, $J = 10.6$ Hz, 2H), 2.53–2.69 (m, 1H), 3.07 (d, $J = 11.2$ Hz, 2H), 3.59 (s, 2H), 5.10 (bs, 2H), 6.51 (d, $J = 5.4$ Hz, 1H), 6.85 (dd, $J = 7.3$, 1.5 Hz, 1H), 7.12 (t, $J = 8.7$ Hz, 2H), 7.23–7.40 (m, 5H), 7.50 (bs, 1H), 7.63 (m, 2H), 8.11 (d, $J = 5.4$ Hz, 1H), 9.42 (d, $J = 7.3$ Hz, 1H). MS (ESI+) 479.4.

*4.1.59.11. 4-[2-(4-Fluorophenyl)-7-(1-phenethylpiperidin-4-yl)-imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-ylamine (**62k**).* Compound **62k** was prepared by Method A from amine **61** (40.0 mg, 0.103 mmol), AcOH (40 μL), phenylacetaldehyde (15 mg, 13 μL, 0.12 mmol at $t = 0$ h, then an additional 2.0 μL at $t = 6$ h), and sodium cyanoborohydride (113 μL of a 1.0 M solution in THF, 0.113 mmol). Yield of **62k**: 38.3 mg (63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.80–1.95 (m, 2H), 1.91–2.00 (m, 2H), 2.20 (bt, $J = 10.8$ Hz, 2H), 2.57–2.74 (m, 3H), 2.82–2.94 (m, 2H), 3.20 (bd, $J = 11.3$ Hz, 2H), 5.10 (bs, 2H), 6.51 (d, $J = 5.4$ Hz, 1H), 6.85 (dd, $J = 7.3$, 1.5 Hz, 1H), 7.12 (t, $J = 8.7$ Hz, 2H), 7.19–7.41 (m, 5H), 7.50 (bs, 1H), 7.59–7.67 (m, 2H), 8.11 (d, $J = 5.4$ Hz, 1H), 9.42 (d, $J = 7.3$ Hz, 1H). MS (ESI+) 493.3.

*4.1.60. 7-Chloro-2-(4-fluorophenyl)imidazo-[1,2-a]pyridine (**63**)*

A solution of 2-amino-4-chloropyridine (2.00 g, 15.5 mmol) and 2-bromo-1-(4-fluorophenyl)ethanone (3.36 g, 15.5 mmol) in EtOH (40 mL) was heated to 60 °C for 12 h. The reaction was then concentrated under reduced pressure, and then chromatographed on SiO_2 using a heptane/EtOAc gradient. Yield of **63**: 700 mg (18%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.98 (dd, $J = 7.1$, 2.0 Hz, 1H), 7.28 (t, $J = 8.6$ Hz, 2H), 7.75 (bs, 1H), 7.95–8.05 (m, 2H), 8.41 (s, 1H), 8.57 (d, $J = 7.1$ Hz, 1H). MS (ESI+) 247.0.

*4.1.61. 1-[7-Chloro-2-(4-fluorophenyl)imidazo-[1,2-a]pyridin-3-yl]ethanone (**64**)*

A solution of imidazopyridine **63** (600 mg, 2.43 mmol) in acetic anhydride (16 mL) was charged with concentrated H_2SO_4 (three drops) and heated to 160 °C for 6 h. The reaction was then concentrated under reduced pressure, and then chromatographed on SiO_2 using a gradient that started with heptane and ended with 30:70 EtOAc:heptane. Yield of **64**: 300 mg (42%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.20 (s, 3H), 7.08 (dd, $J = 7.5$, 1.9 Hz, 1H), 7.21 (t, $J = 8.6$ Hz, 2H), 7.53–7.60 (m, 2H), 7.72 (d, $J = 1.9$ Hz, 1H), 9.70 (d, $J = 7.5$ Hz, 1H). MS (ESI+) 289.0.

*4.1.62. 1-[7-Chloro-2-(4-fluorophenyl)imidazo[1,2-a]-pyridin-3-yl]-3-dimethylaminopropenone (**65**)*

A mixture of ketone **64** (300 mg, 1.04 mmol) in DMF (5.0 mL) was charged with DMFDMA (1.38 g, 10.4 mmol)

and heated to 110 °C for 6 h. The reaction mixture with enone **65** was concentrated under reduced pressured, and then carried onto the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.48 (bs, 3H), 3.07 (bs, 3H), 5.10 (d, $J = 12.4$ Hz, 1H), 6.93 (dd, $J = 7.5$, 2.2 Hz, 1H), 7.14 (t, $J = 8.7$ Hz, 2H), 7.64 (d, $J = 12.4$ Hz, 1H), 7.65 (d, $J = 2.2$ Hz, 1H), 7.65–7.73 (m, 2H), 9.59 (d, $J = 7.5$ Hz, 1H). MS (ESI+) 343.8.

*4.1.63. 4-[7-Chloro-2-(4-fluorophenyl)imidazo[1,2-a]-pyridin-3-yl]pyrimidin-2-ylamine (**66**)*

The reaction mixture described above with enone **65** (theoretically 357 mg, 1.04 mmol) in DMF (5.0 mL and DMFDMA (1.38 g, 10.4 mmol) was charged with guanidine hydrochloride (496 mg, 5.19 mmol) and K_2CO_3 (717 mg, 5.20 mmol). The reaction was heated to 110 °C for 12 h, and was then chromatographed on SiO_2 using a heptane/EtOAc gradient. Yield of **66**: 147 mg (41% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.12 (bs, 2H), 6.53 (d, $J = 5.3$ Hz, 1H), 6.92 (dd, $J = 7.5$, 1.9 Hz, 1H), 7.14 (t, $J = 8.7$ Hz, 2H), 7.60–7.68 (m, 2H), 7.69 (d, $J = 1.9$ Hz, 1H), 8.15 (d, $J = 5.3$ Hz, 1H), 9.48 (d, $J = 7.5$ Hz, 1H). MS (ESI+) 339.8.

*4.1.64. 4-[2-(4-Fluorophenyl)-7-(4-methylpiperazin-1-yl)-imidazo[1,2-a]pyridin-3-yl]pyrimidin-2-ylamine (**67**)*

Nitrogen was bubbled through a solution of imidazopyridine **66** (62 mg, 0.18 mmol) in *N*-methylpiperazine (6.0 mL). After 10 min, 2-(di-*tert*-butylphosphino)biphenyl (8.0 mg, 0.027 mmol), sodium *tert*-butoxide (26 mg, 0.27 mmol) and palladium(II) acetate (4.0 mg, 0.018 mmol) were sequentially added, and the reaction was heated to 100 °C under nitrogen for 12 h. The reaction was then concentrated under reduced pressure, and chromatographed on SiO_2 using a gradient that started with CH_2Cl_2 and ended with 90:9:1 CH_2Cl_2:MeOH:-concentrated NH_4OH. Yield of **67**: 43 mg (58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 3H), 2.60 (t, $J = 4.8$ Hz, 4H), 3.35 (t, $J = 4.8$ Hz, 4H), 5.01 (bs, 2H), 6.49 (d, $J = 5.5$ Hz, 1H), 6.70 (dd, $J = 7.8$, 2.7 Hz, 1H), 6.87 (bs, 1H), 7.12 (t, $J = 8.8$ Hz, 2H), 7.60–7.68 (m, 2H), 8.05 (d, $J = 5.5$ Hz, 1H), 9.41 (d, $J = 7.8$ Hz, 1H). MS (ESI+) 404.2.

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